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HUMAN BIOLOGY
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OSSIFICATION IN A CENTRAL AUSTRALIAN TRIBE *

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INTRODUCTION

So far as can be discovered, there is yet no account of times of ossification in the Australian aborigine. The present study, despite its obvious defects, thus gains some interest from that point of view.

These observations are confined to the members of the Ngalia tribe, together with a very few pure or mixed offspring of neighboring tribes. They were all assembled as a single economic unit in and around the Government Settlement at Yuendumu, some 200 miles northwest of Alice Springs. The "aliens" in the group were not detected until genealogies were checked later. They are indicated in Table I and are included in the results because they show no peculiarities.

Frazer ('33) has pointed out that ossification times differ from people to people and place to place, and are subject to the influence of

* The material upon which this work is based was collected on a University of Adelaide anthropological expedition financed largely by grants from the Wenner-Gren Foundation for Anthropological Research, Incorporated, New York, and the University of Adelaide.

a number of environmental variables. Whether there are, in addition, really significant differences between different ethnic groups still remains to be settled, however.

It is not pretended that the picture presented here is characteristic of the aborigines as a whole. Even given a common hereditary ossification pattern there remains ample scope for substantial differences between these people of the relatively arid interior and those of, say, the more luxuriant north. The present series itself may not be homogeneous from the dietary point of view. The group came under government care only recently. Consequently, while the older members passed their early childhood on a purely native diet, the younger have enjoyed, in addition, access to European food supplements, together with some measure of pre- and postnatal care (see Campbell and Barrett, '53).

Disease may affect bony maturation (Harris, '33). This possibility is not considered here, mainly because of ignorance of the local endemic diseases. Yaws (frambesia) must be fairly common, even in youth, judging from the incidence of "boomerang" or "saber" tibia (plate 1, A), but its effects on growth are unknown. There was no evidence in such people of interference with ossification times.

The number examined were relatively small and age estimations were sometimes uncertain. Consequently, the findings are presented with some reserve. It is hoped that they will stimulate the prosecution of more extensive and better equipped investigations on as many other tribal groups as is still possible.

MATERIAL AND METHODS

The x-ray apparatus employed was a Watson Victor M 1 portable. Power was supplied by a petrol-driven field generator and a portable transformer. The films were 8 inch $\times$ 10 inch "Kodarex" which require no intensifying screen. Exposures were mostly at 30 kv. and 10 to 12 milliamps for 2 to 5 seconds, at a distance of 30 inches. Apart from a field check, development of the films had to be deferred until return to Adelaide but the results were almost uniformly satisfactory.

Because of limitations of time and material, radiographs were restricted to the wrist-hand and ankle-foot regions. Both sides were radiographed simultaneously. All the subjects also underwent a full anthropological and dental examination.

Age estimations presented some difficulty. Only in the case of the very young were there any reasonable records. Even then there was

TABLE I: AGE INCIDENCE

Age Group	MALES		FEMALES	
	Ngalia	Other	Ngalia	Other
< 1 mth.	–	–	1 (3 weeks)	–
1 - 6 mth.	–	–	1 (4 mth.)	–
6-12 mth.	1 (8 mth.)	–	–	–
12-18 mth.	1 (17 mth.)	–	1 (16 mth.)	–
18-24 mth.	1 (20 mth.)	–	–	–
2 - 3 yr.	1 (29 mth.)	–	–	–
3 yr.	3	–	–	–
3 - 4 yr.	–	–	1	–
4 yr.	–	–	1	–
5 yr.	1	–	2	–
5 - 6 yr.	–	–	1	–
6 yr.	1	–	2	–
6 - 7 yr.	1	1 (Aranda x Ngalia)	1	–
7 yr.	5	–	4	–
7 - 8 yr.	1	–	–	–
8 yr.	2	–	2	–
8 - 9 yr.	–	–	2	–
9 yr.	1	1 (Pintubi x Ngalia)	1	–
10 - 11 yr.	–	–	1	1 (Pintubi)
11 yr.	1	–	–	–
11 - 12 yr.	1	–	–	–
12 yr.	1	1 (Aranda x Ngalia)	–	–
13 yr.	–	–	1	–
* 14 yr.	1	–	1	–
14 - 15 yr.	–	–	1	–
15 yr.	–	–	–	–
16 yr.	1	–	2	1 (Pintubi)
17 yr.	–	–	1	–
18 yr.	–	–	1	–
> 19 yr.	–	–	1	–
Totals	24	3	29	2

* This lad was very precocious physically.

Enclosed group is that used for study of foot phalangeal epiphyses

room for an error of several days since, frequently, babies are born while their mothers are on bush excursions, and memory for dates soon fades. All age estimations were checked by such external evidence—mainly physical, and particularly dental—as could be secured. Even with the greatest care, however, there sometimes remained room for error of up to some months.

The excellent kindergarten and school organization on the settlement secured a maximum attendance of the available children from 3 to 11 years of age. On the other hand, there is a regrettable shortage at both ends of the series. The youngest female was 3 weeks of age but the youngest male was 8 months. Obviously, it is misleading to regard these two ages as comparable, but when a center appears before 3 weeks they must be put in anachronistic juxtaposition when trying to establish a *terminus a quo*. There were sufficient adolescent females to provide a reasonable *terminus ad quem* for that sex but most of the adolescent males were out hunting or away in employment, leaving only a very precocious lad of 14 years and another—probably more typical physically—of 16 years.

In dating the results it must be remembered that if a center is already present it must have appeared at an earlier stage: this is indicated by the sign $<$ before the age given. Only occasionally was a center caught at a rudimentary stage that could fairly be assumed as close to its first appearance. If any epiphysis had not fused at the maximum age in the series it was assumed that it would fuse later: this is indicated by the sign $>$ before the age. In the case of epiphyses of metacarpals, metatarsals and phalanges it was possible to determine before complete fusion whether the secondary centers were proximal or distal. After fusion, of course, such distinction is sheer assumption as is, indeed, the postulation of any epiphysis at all. Complete fusion was recorded only when all trace of an epiphyseal line had disappeared. This is later than the standard adopted by Greulich and Pyle ('50) and may set back the apparent time of fusion. However, it seems the only way of being certain that fusion is complete.

The series comprised 27 males, including 3 of mixed parentage, and 31 females of whom 2 were pure Pintubi (a neighboring tribe). Their age incidence is shown in Table I.

SUPERIOR EXTREMITY

TABLE II: Distal Radial and Ulnar Epiphyses

Bone	Appearance		Fusion		Ulnar Styloid	
	M	F	M	F	M	F
Radius	<20 mths.	< 16 mths.	> 16 yrs.	18-19 yrs.	—	—
Ulna	< 5 yrs.	< 5 yrs.	> 16 yrs.	18-19 yrs.	6-7 yrs.	8-9 yrs.

TABLE III: Carpus

Capitate		Hamate		Triquetrum		Lunate Semilunar		Scaphoid Navicular		Trapezium Mult. Maj.		Trapezoid Mult. Min.		Pisiform	
M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
<8 mths.	3 wks.	8 mths. "hook" at 12 yrs.	<4 mths. 11 yrs.	<20 mths.	<16 mths.	<5 yrs.	<4 yrs.	<5 yrs. tubercle at 11-12 yrs.	<4 yrs. 11-12 yrs.	<5 yrs. ridge at 12 yrs.	<4 yrs. 11 yrs.	<5 yrs.	<4 yrs.	<14 yrs.	10-11 yrs.

TABLE IV: Metacarpal Epiphyses

	I		II		III		IV		V	
	M	F	M	F	M	F	M	F	M	F
App.	<20 mths.	<16 mths.	<20 mths.	<16 mths.	<2¼ yrs.	<16 mths.	<2½ yrs.	<16 mths.	<3 yrs.	<16 mths.
Fuse	>16 yrs.	<19 yrs.	<16 yrs.	<19 yrs.	<16 yrs.	<19 yrs.	<16 yrs.	<19 yrs.	<16 yrs.	<19 yrs.

TABLE V: Hand Phalangeal Epiphyses

Phalanx		Dig. 1		Dig. 2		Dig. 3		Dig. 4		Dig. 5	
		M	F	M	F	M	F	M	F	M	F
1	A	<3 yrs.	<16 mths.	<20 mths.	<16 mths.	<20 mths.	<16 mths.	<20 mths.	<16 mths.	<20 mths.	<16 mths.
	F	<16 yrs.	<19 yrs.	<16 yrs.	<19 yrs.	<16 yrs.	<19 yrs.	<16 yrs.	<19 yrs.	<16 yrs.	<19 yrs.
2	A	<20 mths.	<16 mths.	<3 yrs.*	<16 mths.	<20 mths.	<16 mths.	<20 mths.	<16 mths.	<3 yrs.	<16 mths.
	F	<14 yrs.	<19 yrs.	<14 yrs.	<19 yrs.	<16 yrs.	<19 yrs.	<16 yrs.	<19 yrs.	<14 yrs.	<19 yrs.
3	A	–	–	<3 yrs.	<16 mths.	<2½ yrs.	<16 mths.	<2½ yrs.	<16 mths.	<3 yrs.	<16 mths.
	F			<14 yrs.	<19 yrs.	<14 yrs.	<19 yrs.	<14 yrs.	<19 yrs.	<14 yrs.	<19 yrs.

* The male child of 20 months showed this epiphysis, but on the left hand only.

A = appearance. F = fusion.

RESULTS

Superior Extremity

Distal radial and ulnar epiphyses (Table II)

Radius In the male the distal radial epiphysis had not appeared at 17 months (single case) but was present at 20 months (single case). Fusion was not complete in the lad of 16 years. In the female this epiphysis was bilaterally present at 16 months (single case). Fusion was incomplete at 18 years but complete in the woman over 19 years.

Ulna In the male there was no trace of a distal ulnar epiphysis at 3 years. The series did not include a 4 year old male but the epiphysis was well developed bilaterally at 5 years. In the female, the center was absent at 4 years, present at 5 years. Fusion appears to be about the same time as for the distal radial epiphysis.

These times are not markedly different from those found in Europeans.

Carpus (Table III)

The order of ossification of these bones betrays no peculiarities although there is always some inter-variation between trapezium and trapezoid. In the present series one case (No. 2: Pintubi × Ngalia male, aged 9 years) showed apparent retardation on the radial side (right hand only), with the trapezoid ahead of the trapezium (plate 1, C). Another case deserves mention. This (No. 56: a Ngalia male, aged 3 years) showed bilaterally a peculiar center which could be interpreted as either a proximal, additional, epiphysis for the second metacarpal or as a slightly ectopic—and precocious—center for the trapezoid (plate 1, B).

In all instances the female appears to be ahead of the male, both in the appearance of a center and in its maturation as indicated by "facetting," and the development of special characters. Further, while in the male the pisiform center appeared at about the same time as the sesamoids opposite the head of the first metacarpal, in the female the pisiform was 3-4 years ahead of the sesamoids.

No other peculiarities in the way of extra or ectopic centers or bipartite bones were noted. The times of appearance of most of these centers lie within the recorded European range. However, the triquetrum is earlier, as is the appearance of carpal maturation when compared with the figures given by Greulich and Pyle ('50).

Metacarpal Epiphyses (Table IV)

All primary centers were present in the youngest child examined, a female aged 3 weeks. Epiphyses for the first metacarpals were all proximal, those for the remainder all distal—with the possible exception of the second (No. 56) already discussed. There was no trace of any supernumerary digit or other variation and the only sesamoids seen were those opposite the head of the first metacarpal (flexor-abductor and adductor sesamoids).

The time of appearance of these centers in the female is consistently earlier than in the male. Against most European standards (Greulich and Pyle give generally earlier times) all the epiphyses in the female and those of the first and second metacarpals in the male are precocious. Male time of fusion here appears ahead of European, female about the same as European, but the instances are too few for assurance.

Hand Phalangeal Epiphyses (Table V)

All the primary centers were present in the youngest child examined. All the epiphyses observed were proximal; there was none extra or ectopic. In both sexes in both hands the epiphysis of the second phalanx of the thumb was earlier and always larger than that for the first phalanx (plate 1, B, C).

The female adolescent series gave the general order of fusion as distal: proximal: middle. The males were too few to supply much information in this respect. As with the metacarpals, the female seems to be ahead in appearance and behind in fusion, but the series is restricted.

The times of appearance of these epiphyses lie within the European range as given by Greulich and Pyle. The times of fusion may be earlier in the males and later in the females, as compared with Europeans.

Inferior Extremity

All radiographs of the foot-ankle region were taken in the antero-posterior position with the foot plantar-flexed. This secured the maximum "coverage" per film, but in some instances the lower end of the tibia and fibula overlapped the hinder tarsal bones and obscured the picture in that region.

Distal Tibial and Fibular Epiphyses (Table VI)

Tibia In the male the lower epiphysis was already present in the

INFERIOR EXTREMITY.

TABLE VI: Distal Tibial and Fibular Epiphyses.

Bone	Appearance		Fusion	
	M	F	M	F
Tibia	<8 mths.	<4 mths.	<16 yrs.	<16 yrs.
Fibula	<20 mths.	*<3-4 yrs.	<16 yrs.	<16 yrs.

* May have appeared at 16 months, but that plate was obscured in this region.

TABLE VII: Tarsus.

Calcaneum Os Calcis		Talus Astragalus		Cuboid		Cuneiform III		Cuneiform I		Cuneiform II		Navicular Scaphoid	
M	F	M	F	M	F	M	F	M	F	M	F	M	F
<8 mths.	<3 wks.	<8 mths.	<3 wks.	<8 mths. Per. Long notch 7-8 yrs.	*3 wks. 8 yrs.	<8 mths.	<4 mths.	<20 mths.	<3-4 yrs.	<29 mths.	<3-4 yrs.	<29 mths. Tubercle 7 yrs.	*3-4 yrs. >5 yrs.

* Just appearing.

TABLE VIII: Metatarsal Epiphyses.

	I		II		III		IV		V	
	M	F	M	F	M	F	M	F	M	F
App.	<3 yrs.	<3-4 yrs.	<3 yrs.	<3-4 yrs.	<3 yrs.	<3-4 yrs.	* 3 yrs.	<3-4 yrs.	<5 yrs.	<3-4 yrs.
Fuse	<14 yrs.	<19 yrs.	<16 yrs.	<18 yrs.	<14 yrs.	<18 yrs.	<14 yrs.	<18 yrs.	<14 yrs.	<18 yrs.

*Just appearing.
Note: Metatarsal V styloid. Male at 6-8 yrs. Female at 5-7 yrs.

TABLE IX: Foot Phalangeal Epiphyses.

Phalanx		Dig. 1		Dig. 2		Dig. 3		Dig. 4		Dig. 5	
		M	F	M	F	M	F	M	F	M	F
1	A	29 mths.	16 mth.	<20 mth.	<16 mth.	<20 mth.	<16 mth.	<20 mth.	<16 mth.	<3 yrs.	<16 mth.
	F	<16 yrs.	<16 yrs.	>16 yrs.	>19 yrs.	16 yrs	<19 yrs.	16 yrs.	<19 yrs.	>16 yrs.	<19 yrs.
2	A	20 mth.	<16 mth.	<20 mth.	<3-4 yrs.	<20 mth.	<4 yrs.	<3 yrs.	?<3-4 yrs.	? 3 yrs.	?<3-4 yrs
	F	<16 yrs.	14-17 yrs.	14 yrs.	>16-18 yrs.	14 yrs.	<16 yrs.	14 yrs.	<16 yrs.	<14 yrs.	<16 yrs.
3	A	-	-	3 yrs.	<3-4 yrs.	<3 yrs.	<3-4 yrs.	<3 yrs.	<3-4 yrs.	? 3 yrs.	?<3-4 yrs
	F			14 yrs.	14-16 yrs.	14 yrs.	<16 yrs.	14 yrs.	<16 yrs.	<14 yrs.	<16 yrs.

A = Appearance. F = Fusion.

youngest examined—8 months. In the female the center appeared between the third week and the fourth month. In both sexes time of fusion was about the same but was obscured by the overlapping referred to above.

Fibula In the male the lower epiphysis was present before 20 months. In the female it may have been present at 16 months, but the radiograph for the individual of that age was obscured and the next—3 to 4 years—is the earliest that can be cited. Time of fusion appeared to be about the same for both sexes but estimates are subject to the same limitations as for the tibia.

These figures show no clear-cut sexual distinction. In both sexes both bones fall within the maximum European range as given by Meschan ('51).

Tarsus (Table VII)

The fact that the major centers for the calcaneum and talus were already well present in the youngest child examined (3 weeks) supports the contention that these centers—as in Europeans—appear before birth. In the same child the condition of the cuboid was consistent with the view that its center appeared at or just after birth. The navicular falls within European extremes. The order of ossification of the cuneiforms is an accepted variant but the times are early. Maturation, as indicated by characteristic sculpturing and the appearance of distinctive features, is generally earlier in the male but otherwise there is little sexual differentiation.

There was no evidence of a special center for an os trigonum on the talus, an epiphysis on the calcaneum or the tubercle of the navicular, nor were any unusual centers discovered. The female aged about 19 years had bilateral tibialis posterior sesamoids.

Metatarsal Epiphyses (Table VIII)

All primary centers were present in the youngest child examined (3 weeks). The epiphysis on the first metatarsal was always proximal that on the remainder always distal. No ectopic or extra centers were observed and there was no separate center for the tubercle (styloid process) of the fifth metatarsal.

Taken all round, the female may be ahead of the male in times of appearance of these centers but there is little evidence except, perhaps, for the fifth metatarsal. The times are close to those given for Euro-

peans. Fusion appears to be earlier than in Europeans in the male, later in the female, but again the evidence is scanty.

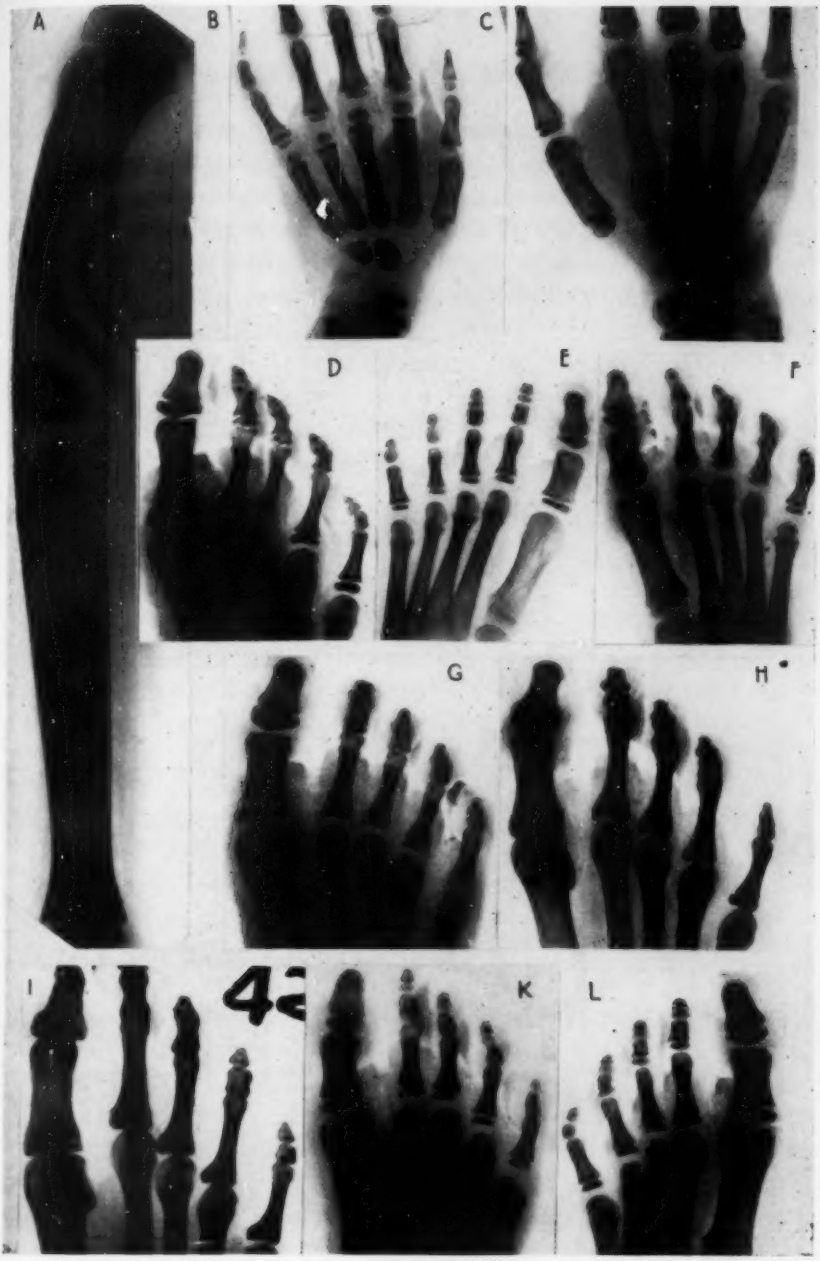
Foot Phalangeal Epiphyses (*Table IX*)

All primary centers were present in the youngest child. So far as could be determined the epiphyses were proximal except for a possible variant in the little toe, mentioned below. In the big toe in both sexes—as in the thumb, but to a lesser extent—the epiphysis of the second phalanx appeared earlier, and was always larger than the epiphysis of the first phalanx (plate 1, E, F).

Table IX gives times of appearance and fusion for all the epiphyses of all the toes but it should be emphasized that not a single foot attained this ideal. In both sexes in all feet both phalanges of the first toe, and the first phalanges of all the other toes, behaved in " text-book " fashion. However, the middle and distal phalanges of the second, third, fourth and fifth toes were subject to considerable variation. This is shown in Tables X and XI. Here the age group is chosen to ensure inclusion of all epiphyses likely to appear (Table I). The males (aged 5 to 12 years) and females (aged 4 to 13 years) are approximately equal in numbers.

It will be noted that from the second toe laterally there is a progressively greater tendency to suppression of epiphyses in the middle and distal phalanges (Table X). Either phalanx, or both, may be involved but the middle is affected more than twice as often as the distal. It is also apparent that the incidence is much greater in the females in whom more than half had all 4 lateral toes affected and more than three-quarters had at least three toes involved. The male, on the other hand, more frequently showed involvement of only one or two toes.

In neither foot of either sex was there a little toe with its full complement of bony elements. Moreover, the bones present varied considerably in size and shape and often bore little resemblance to either primary or secondary centers (plate 1, D-L). Such bony fragments are best referred to as ossicles. The maximum possible number of such ossicles in the distal two joints would be 4: in fact, in no little toe were more than three observed, two was the commonest number, but one alone occurred occasionally (Table XI). There has evidently been some suppression (or, possibly, very premature fusion) of some centers, but exactly which is not always clear. Thus the middle of three ossicles may, apparently, behave like the epiphysis of the distal phalanx and



A. "Boomerang" tibia. No. 58, Ngalia girl aged 6-7 years.
B. Ectopic trapezoid or proximal epiphysis at base of second metacarpal. No. 56, Ngalia boy aged 3 years.
C. Retardation of radial side of carpus, putting trapezoid ahead of trapezium. No. 2, Ngalia × Pintubi boy, aged 9 years.
D. Three ossicles in little toe. No. 71, Ngalia girl, aged 13 years.
E. Two ossicles in little toe. No. 73, Ngalia boy, aged 7 years.
F. One ossicle in little toe. No. 53, Ngalia girl, aged 4 years.
G. One ossicle in little toe. No. 3, Ngalia boy, aged 9 years.
H. One ossicle in little toe. No. 78, Ngalia girl, aged 16 years.
I. Two ossicles in little toe. No. 42, Ngalia girl, aged 16 years.

(The last three figures are reproduced here to illustrate the point that deficiency of ossicles in childhood is not necessarily corrected during maturation.)

K. The proximal ossicle in the little toe gives the appearance of representing the middle and proximal fused together. No. 98, Ngalia boy, aged 7 years.
L. The distal ossicle in the little toe gives the appearance of representing the middle and distal ossicles fused together. (This is much less common than K.) No. 47, Ngalia boy, aged 7 years.

Note: scrutiny of figures D to L discloses many different grades of epiphyseal suppression in the lateral four toes.

fuse with that or, more commonly, act as the diaphysis of the middle phalanx and treat the proximal ossicle as an epiphysis (plate 1, K, L). That, at least, is what examination of these radiographs suggests but a longitudinal series would be necessary to be sure in any one case.

A point of interest is that these osseous changes in the feet were nearly always symmetrical.

SUPPRESSION OF BONY ELEMENTS IN FEET of 18 Males, aged 5-12 yrs. and 19 females, aged 4-13 yrs.

TABLE X: Number of Toes Affected.

5th Only		5th & 4th		5th, 4th & 3rd		5th, 4th, 3rd & 2nd		Uncertain		Totals	
M	F	M	F	M	F	M	F	M	F	M	F
4	1	5	1	4	5	3	10	2	2	18	19

TABLE XI: Number of Phalanges Affected.

	Suppression of Epiphyses						Ossicles only*	5th Toe		Uncertain	
	2nd Toe		3rd Toe		4th Toe						
Phalanx	M	F	M	F	M	F		M	F	M	F
Distal	3	5	2	0	0	0	3	5	5	2	2
Middle	0	5	3	13	9	10	2	12	11		
Both	0	0	2	1	3	6	1	1	1		

* See text concerning 5th toe.

DISCUSSION

Despite some unfortunate gaps in the evidence a few conclusions of interest emerge. In the first place, the times of ossification displayed by the aborigine lie within the total European range as given in standard works by Quain ('15), Frazer ('33), Buchanan ('49), Gray ('49), Greulich and Pyle ('50), Cunningham ('51), Meschan ('51), and others. The most that can be said for the aborigine is that he

usually falls into the earlier part of the range. This would be in line with Campbell's ('25) observations on the generally earlier dental maturation in aborigines.

Most writers emphasize that in any ethnic group the female both begins and ends ossification earlier than the male. The figures for the aborigine generally support the contention for an earlier start in females, but what evidence there is suggests a later finish. Here, however, the facts are so scanty that it would be unwise to insist upon the reliability of this interpretation.

One of the most striking results of this—admittedly limited—survey is the almost complete absence of a wide range of possible bony variations as described for the European foot (see, e. g. Wood Jones, '44).

In default of any positive evidence for specific ethnic peculiarities, attention may be directed to what seems to be the most interesting outcome of this study, namely, the evidence for "degeneration" or "recession" on the lateral side of the foot. It is something of an article of faith that such a process is occurring in the European foot, but details are hard to find in standard works on anatomy and even in books devoted entirely to the foot. These all seem to contain an underlying assumption that the full number of bony elements is the rule and that any deficiencies of the moment are the result of delay, to be repaired in time. However, Flecker ('32) has shown that this is not necessarily the case. For urban children of mostly European parentage he reports a condition very similar to that described here for the aborigine, and with the same heavier incidence in the female.

When it receives any attention at all, this suppression of osseous elements in Europeans is usually attributed to the effects of civilized existence and, particularly, footwear. The greater female incidence has been considered confirmatory evidence. But, the fact that the same phenomenon appears at an equal intensity, and with a similar sexual distribution, in aborigines who have never known civilized life or footwear exculpates both factors as possible agents. The process, then, must be part of a common human heritage, associated with increased emphasis upon the medial side of the foot in the interests of stability. The greater intensity in females may reflect special stresses imposed by the broader pelvis and associated bony adjustments.

SUMMARY

1. This paper records the radiological condition of the wrist-hand, ankle-foot regions in 58 Central Australian aborigines of ages from 3 weeks to 19 years.
2. The study as a whole disclosed no ethnic peculiarities.
3. Ossification falls within the time range assigned to Europeans but usually towards the earlier rather than the later limit.
4. An account is given of phalangeal " degeneration " in the foot similar to that found in Europeans.

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FACTORS OF DOSAGE AND HOST DETERMINING ANTIBODY RESPONSE TO SECONDARY ANTIGEN STIMULUS [1]

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A SECONDARY antigen stimulus, according to Glenny and Südmersen ('21) is defined as the injection of antigen into an actively immunized animal. The active immunization may be due to natural infection or to artificial immunization with the same specific antigen. The individual may or may not show evidence of such previous treatment by presence of specific antibody in the serum. The effect of a secondary stimulus is a distinctively higher immune response than that of a primary stimulus. Smaller doses of antigen are necessary to produce a secondary response, than those needed for a primary response.

The primary stimulus, however, is preferred in assays of the relative potency of toxoids, because greater uniformity of response is expected from a non-immune population. In field trials of toxoids in human population samples, one is often faced with a mixture of partly immune and non-immune individuals, so that the interpretation of the response is equivocal. Accurate information of previous immunization is often essential for a reduction of the variability through covariance. The following presentation is an attempt to evaluate the importance of measurable independent variables and their contribution to the variation in secondary response in human beings.

Response is in this work measured by the antibody titer which is one measurement of immune response. Other response measurements such

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as percentage of survivals or percentage of skin reactions to antigen or toxin, are less informative since they have the limitations of all-or-non-reactions. A fundamental relationship between antitoxin titer and all-or-non-reactions has been well substantiated recently by Holt ('53), and Cavalli-Sforza ('47).

The discussion is limited to the antitoxin titer at a certain time after the antigen injection, which approximates the time of maximum response. The quality of the antitoxin which recently was subjected to intense study by Jerne ('51) is also omitted from this discussion, where antitoxin titer simply denotes the highest dilution of a serum which neutralizes a given dose of toxin to a certain end-point reaction. Since the titers are uniformly determined throughout the assay, this study deals with comparison of response, where the absolute value of the response is unimportant. The notation of the titers in Antitoxin Units per ml (AU) is in conformity with present convention.

Titrations were performed in mice with constant toxin doses and serial 1:2 dilutions of serum.

For a complete analysis of the factors determining a given secondary response the following variables must be included in the experiment and each must be varied over a sufficiently wide range.

1. (y) The dependent variable which is the titer found after the secondary stimulus. Use of logarithm increases the homoschedasticity of the system somewhat, but there is a tendency of larger error at smaller antitoxin levels.

2. The independent variables are:

   a. (z) The size and potency of the secondary stimulus, also transformed into logarithms.

   b. (x_2) Intensity of previous immunization, which includes the dose and potency of earlier antigen exposure and the time elapsed since it was administered.

   c. (v) Pre-immunization titer, i. e., the antitoxin titer of the individual immediately before the secondary dose is given.

   d. (x_1) The inherent ability of the individual to react to an antigen stimulus. This factor can only be assigned qualitatively to groups of subjects with given species characteristics or some somatic abnormality.

The immunization history, the pre-immunization titer and the inherent immunizability together form the immune status. Rarely all the

information is available in a human field study. Accurate knowledge of the time and size of previous injection is often missing, so that subdivisions such as "number of injections," "time since last injection," etc., are the only measurable qualities. The pre-immunization titer is sometimes considered a unique measure of the immunization history. Although a high titer suggests effective previous immunization, low titers or titers below the measurable limits may represent all sorts of immune status including the so-called "non-immune" where an antigen injection would provoke a primary response only. The uncertainty as to whether a person has primary immunity is larger in case of diphtheria than of tetanus, since natural immunity is possible in diphtheria while artificial immunization is the only possible way of acquiring tetanus immunity.

Immunizability is measurable as a group phenomenon rather than as an individual characteristic. It can be shown that animal strains of various genetic composition require different doses of antigen to provoke primary response. Thus, we have been able to show that two pure inbred strains of mice differ 12 times in the amount of tetanus toxoid necessary to induce 50% primary immunity to challenge with tetanus toxin. Similar differences were noted in guinea-pigs with respect to diphtheria immunizability (Prigge, '35; Scheibel, '43).

The influence of inherent immunizability on secondary response needs systematic research. The experimental data to be presented afford an opportunity to analyze the four components of primary dose, pre-immunization titer, secondary dose and inherent immunizability in a group of young men. It was possible to conclude that primary dose and primary response were interchangeable measurements and that immunizability is a property which is more pronounced in secondary response than in primary response.

EXPERIMENTAL DATA

The experiment was originally designed to assay the relative potency of four aluminum precipitated toxoids. The subjects were inmates of the Wrentham State School, Massachusetts, of which 128 young men, aged 15-25, were selected because of no previous history of tetanus immunization, which was furthermore confirmed by the fact that none of the subjects showed measurable antitoxin in the blood before the test. Each of the four toxoids were given in either of two doses, 0.1 ml and 0.5 ml, respectively. These eight treatments were repeated 4 weeks after the first injection, but the individuals were distributed according to an 8×8 latin square with the primary injections forming one axis, and the

TABLE 1

Primary (v) and Secondary Titer (y) (in log antitoxin + 3) for 128 Individuals, by Primary and Secondary Dose of Tetanus Toxoid

SECONDARY DOSE OF TOXOID	(ml)	z	PRIMARY DOSE OF TOXOID: Toxoid A 0.1 ml 0.2		Toxoid A 0.5 ml 0.9		Toxoid B 0.1 ml 0.9		Toxoid B 0.5 ml 1.6		Toxoid C 0.1 ml 0.5		Toxoid C 0.5 ml 1.2		Toxoid E 0.1 ml 0.0		Toxoid E 0.5 ml 0.7 (x_3)	
			v	y	v	y	v	y	v	y	v	y	v	y	v	y	v	y
A	0.1	0.2	0.1†	3.3†	0.1	1.7	0.1	2.0	1.0	2.3	0.1*	0.1*	1.6	3.5	0.1	1.7	0.1	1.0
			0.1	3.2			0.4	2.0	1.6	2.6	0.1	2.0	0.4†	3.2†	0.1	2.9	0.1	2.6
	0.5	0.9	0.1	2.0	0.1	2.6	0.1*	2.3*	1.3	3.2	0.1	3.2	2.2	1.7	0.1*	1.4*	0.1	1.7
			0.1	2.6	0.1	3.5	0.1	1.1	1.0*	2.6*	0.4	3.2	1.3	3.2	0.1	2.3	0.1*	2.9*
													0.1	2.9			0.4	2.3
B	0.1	0.9	0.1	3.5	2.2	3.6	0.1	1.1	1.6	2.6	0.1	2.9	1.9	2.3	0.1	2.3	0.1	2.6
			0.1	3.2	0.1	2.9	0.1	1.4	0.7	2.6	0.1	2.9	0.1	2.9	0.1	2.0	1.6	2.9
	0.5	1.6	0.1*	3.6*	0.1*	3.9*	1.0	2.9	1.9	3.2	0.1	3.6	0.7	3.2	0.1	2.6	0.4*	3.9*
			0.1	3.2	0.4	2.9	0.1	2.9	1.3	3.5	0.1*	2.9*	1.0	3.6	0.1	2.9	0.1	3.2
							0.1*	3.2*			0.7	3.3						
C	0.1	0.5	0.1	2.9	0.1	2.3	1.6	2.9	1.6	2.6	0.1	3.5	1.6†	2.9†	0.1	1.1	2.2†	2.6†
			0.1	1.7	0.7	2.3			0.4	1.7			0.4	3.2	0.1	2.0	0.1*	3.2*
	0.5	1.2	0.1	3.2	1.0	2.9	0.1	3.2	0.7*	2.6*	1.0	2.6	1.9	2.0	0.1	2.3	0.1	3.2
			0.4	3.9	0.7	2.9	1.3	2.6	0.7	2.6	0.1	3.2	0.1	2.6	0.1*	2.3*	0.1	2.6
					0.1	3.5												
E	0.1	0.0	0.1	0.1	1.3	3.2	1.0	3.2	0.7	2.0	0.1	1.4	0.1	2.6	0.1*	0.1*	0.1	1.4
			0.1*	1.1*	0.1	2.9	1.9	2.9	1.6	2.3	0.1*	0.1*	0.1	2.6	0.1	0.7	0.7*	2.0*
	0.5	0.7	0.1*	0.1*	0.4	2.9	0.1*	1.4*	1.9	3.2	0.1†	3.9†			0.1	0.1	0.1*	2.6*
			0.1	2.0	0.1	3.5	0.7	2.6	0.4*	1.4*	0.1	3.5	0.7	1.0	0.1	2.0		

* Mongoloids. † Dysendocrines.

0.1 indicates values less than lower limit of titration (0.00125 AU).

secondary injection forming the other axis. Thus all 64 combinations of primary and secondary injections were given. (See table 1.)

The columns of table 1 contain the antitoxin titer (in logarithms plus 3). In the left hand part of each column (v) are those titers determined 28 days after the first injection; in the right hand part are the titers 14 days after the secondary injection (y).

RELATIVE POTENCY OF DOSAGE

A previous report on these data, (Ipsen, '53A), dealt with the estimate of the relative potency of these four toxoids, which had also been assayed in both mice and guinea-pigs. The potency estimates were obtained from this assay in humans by construction of reaction curves relating primary response (v) to dose of toxoid.

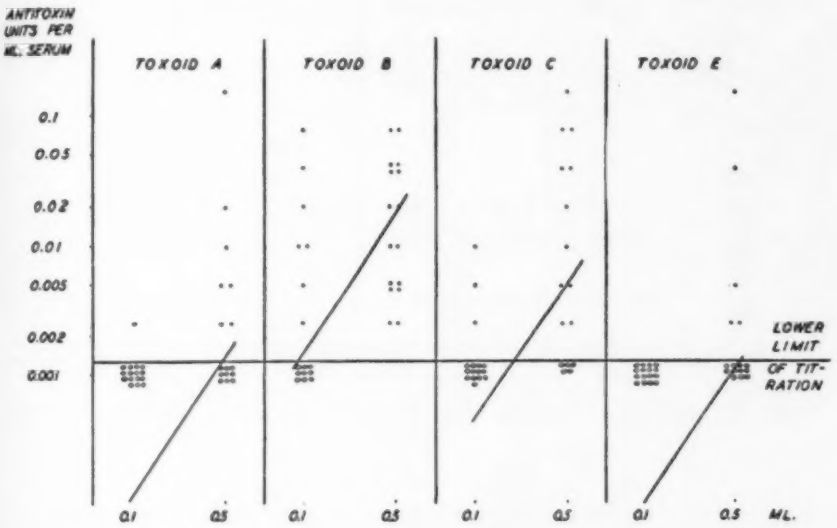

FIG. 1. REACTION CURVES OF FOUR TETANUS TOXOIDS IN HUMANS (PRIMARY RESPONSE)

The reaction curves clearly place Toxoid B as the most potent, Toxoid C of average potency, and A and E as the least potent. The same potency relationship was also found to hold when the secondary responses were related to the secondary dose.

In this particular design each of the groups which received a secondary dose consisted of individuals who had the same average primary

0.1 indicates values less than lower limit of titration (0.00125 AU).

immunity status. Hence, no correction for primary immunity is necessary for the estimation of relative potency based on secondary response.

The eight treatments can now be placed in order of relative potency as indicated in table 2. It should be noted that the potency order of the same four toxoids was found to be identical to that determined in mice and in guinea-pigs.

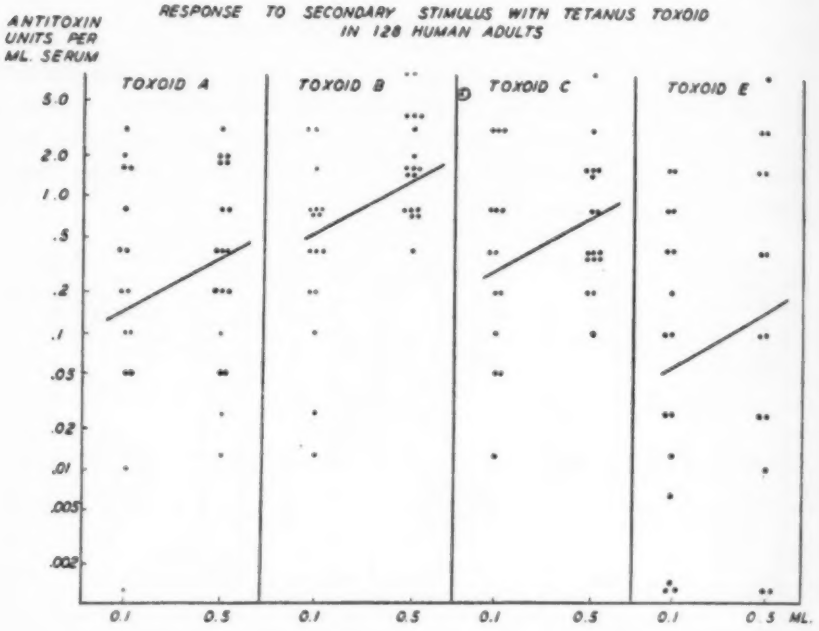

FIG. 2. REACTION CURVES OF FOUR TETANUS TOXOIDS (SECONDARY RESPONSE)

TABLE 2

Mean Primary and Secondary Response, by Potency of Toxoid Dose

Toxoid	Dose	Relative Potency	Log Rel. Potency	Number	Primary Response	Number	Secondary Response	Primary Response*
E	0.1 ml	1.0	0.0	16	0.100	16	1.79	0.51
A	0.1 ml	1.6	0.2	16	0.119	15	2.27	0.40
C	0.1 ml	3.2	0.5	16	0.213	14	2.49	0.66
E	0.5 ml	5.0	0.7	16	0.400	14	2.16	0.36
A	0.5 ml	8.0	0.9	16	0.475	18	2.48	0.43
B	0.1 ml	8.0	0.9	16	0.550	16	2.61	0.57
C	0.5 ml	16.0	1.2	16	0.888	17	2.84	0.51
B	0.5 ml	40.0	1.6	16	1.150	18	3.25	0.47

* Mean titer of group before secondary dose was injected.

REGRESSION ANALYSIS OF PRIMARY AND SECONDARY DOSAGE, DISREGARDING IMMUNIZABILITY

For the biometric analysis, we shall use y (log. secondary antitoxin titer) as the dependent variable, and let the above logarithmic relative potencies substitute for x_2 and z, as measurements of the primary and secondary dosage.

Before assumptions can be made as to primary immunizability, a multiple regression analysis was performed with linear and quadratic terms of x_2 and z and their interactions. Only three terms were found

TABLE 3

Matrix of Sums of Squares and Sums of Products of Deviations from Mean

128 Observations

	z	x_2	zx_2	x_1	zx_1	y
z	31.56					24.91
x_2	0.12	30.40				11.25
zx_2	42.39	23.04	42.39			22.24
x_1	−2.95	1.80	−1.82	24.00		12.31
zx_1	−8.12	0.38	−5.17	17.68	20.39	−2.24
y						100.2437
Means	0.778	0.750	0.580	−0.125	−0.120	2.507

	z	v	zv	x_1	zx_1	y
z	31.56					24.91
v	−0.21	46.11				12.79
zv	15.07	34.21	42.42			15.02
x_1	−2.95	7.39	4.13	24.00		12.31
zx_1	−8.12	5.60	2.20	17.68	20.39	−2.24
Means	0.778	0.487	0.377	−0.125	−0.120	2.507

50 Observations (v larger than 0.1)

	z	v	zv	x_1	zx_1	y
z	12.83					5.03
v	−1.59	16.25				0.96
zv	12.07	10.96	24.13			3.88
x_1	−1.59	3.38	1.01	7.92		1.69
zx_1	−1.65	3.81	0.86	7.45	8.39	0.40
y						18.3442
Means	0.806	1.090	0.847	−0.040	−0.064	2.746

TABLE 4

Analysis of Variance

Primary Dose (x_2), Secondary Dose (z) and Immunizability (x_1)

Component	Sum of Squares	D. F.	Mean Square
Total (y)	100.2437	127	
Regression on z	19.6615	1	
Additional regr. on x_2	4.0898	1	
— interaction x_2z	3.2442	1	
	73.2482	124	0.5902
Additional regr. on x_1	7.5678	1	
— interaction x_1z	4.5401	1	
Remainder	61.1403	122	0.5011

Primary Response (v), z and x_1

Total (y)	100.2437	127	
Regression on z	19.6615	1	
Additional regr. on v	3.6398	1	
— interaction vz	4.2811	1	
	72.6613	124	0.5860
Additional regr. on x_1	6.5125	1	
— interaction x_1z	4.9122	1	
Remainder	61.2366	122	0.5019

50 Individuals Having v Larger Than 0.1

Total (y)	18.3442	49	
Regression on z	1.9693	1	
Additional regr. on v	.1566	1	
— interaction vz	1.3829	1	1.1320
Additional regr. on x_1	.5786	1	
— interaction x_1z	1.5727	1	
Remainder	12.6841	44	0.2883

significant (see table 4, Analysis of Variance) so that a preliminary expectancy equation was computed.

$$y = 1.243 + 0.870x_2 + 1.286z - 0.667x_2z \cdot \cdot \cdot \qquad (1)$$

on the basis of the matrix of sums of squares and sums of products of deviations. (see table 3).

The fit of this expectancy for the overall sample of 128 individuals was next tested for smaller groups. Since the inmates of the institution represented a great variety of constitutions, it was pertinent to investigate whether grouping of the individuals in categories of their somatic and mental diagnosis would reveal any group which deviated in response from the overall expectancy to suggest abnormal immunizability of the group.

TABLE 5

Observed and Expected Means for Ten Diagnostic Categories. Expectation from Equation (1), Disregarding Inherent Immunizability, and from Equation (2), Including Group Immunizability

DIAGNOSTIC CATEGORY	Number n	Observed Mean	Equation (1) Expected Mean	Equation (1) "Student's" t^*	Equation (2) Expected Mean	Equation (2) "Student's" t^{**}
Undiff. imbecility	44	2.49	2.50	—0.04	2.54	—0.43
Familial morons	31	2.65	2.55	+0.70	2.59	+0.43
Central nerv. syst. malformations	5	2.90	2.76	+0.41	2.77	+0.41
Epilepsy and other defects	6	2.60	2.27	+1.03	2.36	+0.83
Psychosis and mental deficiency	6	2.20	2.52	—1.03	2.56	—1.26
Post-traum. idiocy	6	2.82	2.66	+0.49	2.72	+0.32
Post-infect. idiocy	4	2.38	2.49	—0.30	2.55	—0.49
	102	2.56	2.52	+0.51	2.56	—0.09
Mongoloids	21	2.08	2.49	—2.04	2.07	+0.05
Dysendocrines	5	3.18	2.23	+2.52	3.15	+0.11

$$^*t^2 = \frac{(\text{Obs-Exp})^2 n}{0.5907} \qquad ^{**}t^2 = \frac{(\text{Obs-Exp})^2 n}{0.5011}$$

Table 5 shows the observed and expected group mean for ten major categories which were classified by the medical staff of the institution, before the immunization program started.

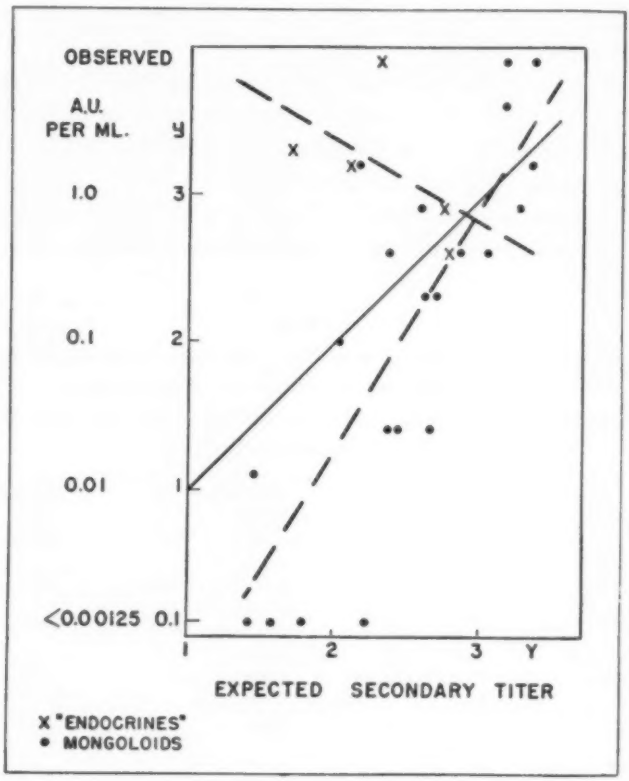

FIG. 3. OBSERVED RESPONSES OF 21 MONGOLOIDS AND 5 "DYSENDOCRINES" IN RELATION TO VALUES EXPECTED FROM EQUATION 1

While the observed titers of eight categories, composing 102 persons, agree well with expectancy equation (1), there are two groups which deviated to the borderline of significance. Mongoloids (21 persons) have a too low response, and "dysendocrines" (5 persons) show an excessive response.

A further analysis of the deviations from expected values within the two groups show that deviations are largest from low expectancies, while high expectancies give acceptable fits.

That mongoloids have less immune response than other individuals is evidenced in studies by Siegel ('48). The group " dysendocrines " is not a well defined one but since it seems to represent an immunological antipode to the mongoloids, it is worth including it in an analysis of immunizability.

Since the two abnormal groups have approximately the same numerical deviation, the immunizability can be tested as a linear regression by assigning the factorial $x_1 = +1$ to the dysendocrines, $x_1 = -1$ to the mongoloids, and $x_1 = 0$ to the remainder categories. The matrix of table 3 contains the significant components; others were also tested, such as the interaction x_1x_2 without giving additional information. The significance of the factor x_1 and its interaction with z is brought out in the analysis of variance. Table 4.

With the solutions of the regression coefficients the expectancy equation now takes the form:

$$y = 1.549 + 0.636x_2 + 1.001z - 0.435x_2z + 1.197x_1 - 0.872x_1z \cdots \quad (2)$$

Equation (2) can be rearranged in the form:

$$y = 1.549 + 0.636(1.88x_1 + x_2) + 1.001z - 0.435z(2.00x_1 + x_2) \cdots \quad (3)$$

which indicates that the inherent factor x_1 has about equal additive effects to the dual functions of the primary dose x_2: one of increasing the secondary response, the other of decreasing the regression of the secondary dose z on the response.

The different contribution of the primary dose and of the immunizability is clearly shown in Figure 4 which presents the observed data in relation to the expected regression lines of y and z for four groups.

The upper line represents the expectancy for the 5 dysendocrines who received an average primary dose of $x_2 = 0.76$, which inserted in equation (2) together with $x_1 = 1$, gives

$$y = 3.26 - 0.200z \cdots \quad (4)$$

The lowest line represents the equation for the mongoloids, where $x_2 = 0.67$ and $x_1 = -1$ leading to

$$y = 0.719 + 2.162z \cdots \quad (5)$$

The two intermediate lines are the expectancy for two primary dose levels of the 102 " normals," of which the upper is the expectancy for 47 individuals with relative high primary dosage ($x_2 = 1.14$) and the lowest line represents 55 persons with a lower primary dose ($x_2 = 0.33$).

The equations are, respectively:

$$y = 2.274 + 0.505z \cdots \quad (6)$$

and

$$y = 1.759 + 0.857z \cdots \quad (7)$$

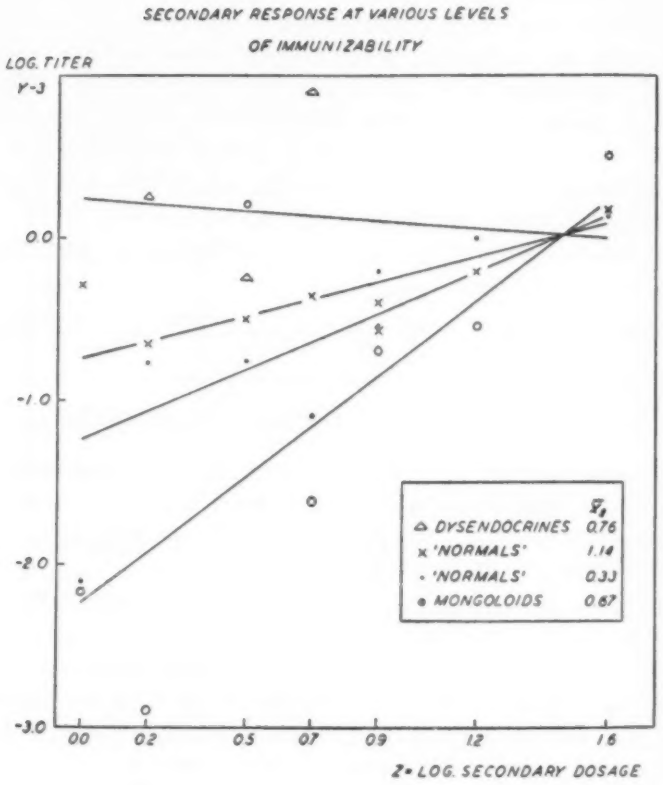

FIG. 4. SECONDARY RESPONSE OF THE VARIOUS IMMUNITY LEVELS, RELATED TO SECONDARY DOSE

The difference between the two "normal" groups is much less pronounced than the difference between the mongoloids and dysendocrines who had approximately the same primary dosage. The points represent the mean of 1-8 individuals of the same kind and with same secondary dosage.

DIFFERENCE IN IMMUNIZABILITY AT PRIMARY STIMULUS

The difference in the two somatic groups amount to about $2 \times 1.88 = 3.76$ in terms of log. primary dose as estimated from the secondary response (equation (3)). This means that the mongoloids would need about 5600 times more potent primary stimulus than the dysendocrines in order to obtain the same responsiveness to secondary stimulus.

This difference is in contrast to the difference in inherent immunizability which can be estimated from the primary response.

The following data are available for the response (v) of the three groups after the first injection, and are presented in table 6.

TABLE 6

Primary Response in Three Groups of Different Immunizability

Group	Number	Average Primary Dosage	Percent with Measurable Antitoxin	Mean Primary Response ($\bar{v}$)
"Normals"	102	0.77	41.2%	0.521
Mongoloids	21	0.67	23.8%	0.229
Dysendocrines	5	0.76	60.0%	0.880
Difference in Immunizability Mongoloids vs. Dysendocrines (in terms of primary dosage)			0.35 ± 0.31	0.79 ± 0.40

The difference in primary response is noticeable, but hardly significant, and even with the large error involved, the difference is nowhere near the extreme difference of 3.76 found from the secondary response of the two groups.

This discrepancy between estimates of immunizability obtained by primary and by secondary response needs further study, which we are now pursuing in inbred mouse strains. (Ipsen, '53B).

RELATION OF PRIMARY RESPONSE TO SECONDARY RESPONSE

The foregoing analysis showed that information of both inherent immunizability and of the primary immunization is necessary to form estimates of the response to a certain secondary dose.

The question now arises whether the primary response gives enough information of both the primary dose and the inherent immunizability,

so that the primary response can be used as an efficient covariance to the secondary response.

The procedure used in the analysis was the same as used above, only the primary response (v) is used instead of the primary dosage (x_2).

Those primary titers which were below the limit of measurement were assigned the value 0.1 (as indicated in table 1).

The matrix of sums necessary for the multiple regression analysis is found in table 3. The solutions of the regression coefficients and the means lead to the following expectancy equation:

$$y = 1.747 + 0.567(v + 2.07x_1) + 0.917z - 0.497z(v + 1.74x_1) \cdots \quad (8)$$

This equation has almost the same form as equation (3) with insignificant difference between the coefficient of x_2 and v. It is particularly noteworthy that the coefficients of x_1 are of the same magnitude in both equations. The analysis of variance (table 4, lower part) shows that x_2 and v give almost equivalent information, while the components of x_1 are of same order of magnitude.

In other words, a given primary antitoxin titer reflects the amount of previous exposure to antigen but it does not predict the full extent of the response to a secondary stimulus.

Since only 50 of 128 individuals had measurable antitoxin after the first dose, it is possible that the relationship expressed in equation (8) is biased because of the large number of v values which have been assessed the limit value of 0.1.

In those persons where the primary titer can be measured, the effect of the inherent immunizability might be included in the primary titer. However, the equation obtained with these 50 individuals has the form:

$$y = 1.61 + 0.72(v + 1.80x_1) + 1.27z - 0.82z(v + 1.34x_1) \cdots \quad (9)$$

which is not significantly different from equation (7) obtained from all 128 samples.

The analysis of variance (table 4) shows that the components due to x_1 are at least as important as those due to v. Hence, it is concluded that inherent immunizability is a function which is independent of the primary response.

DISCUSSION

In the attempt to analyse the variables which influence the secondary response, the procedure has been restricted to analysis of linear components. The true functional equations are probably exponential func-

tions with curves tending toward asymptotes at high values of the respective variables. Such functions are not amenable to explicit regression analysis, and no increase in information was obtained by adding higher terms of a polynomial expansion. The three measurable variables:

(z) potency of secondary dosage

(x_2) potency of primary dosage

(v) antitoxin before secondary immunization

were all found to have some relation to the secondary response. The correlation, however, vanishes at high values of all or either of the variables.

It was further possible to recognize two somatic groups of individuals which deviated from the general expectancy in positive and negative directions, respectively. This discrepancy is ascribed to inherent factors, termed immunizability. While the primary response barely disclosed deviating immunizability, the factor was significantly noticeable after secondary stimulus.

Because of the inhomogeneous character of the population used in this study it is highly likely that other individuals than the dysendocrines and the mongoloids have deviating inherent immunizability; however, these groups were the only ones which could be separated *a priori* on the basis of the available information. Other categorization, such as blood type, was tried with no result.

Bio-assays based on secondary response are feasible, but they meet more obstacles than assays based on primary response.

The restrictions are:

1. Small secondary doses only will give significant regression of response on dose. What should be classed "small dose" depends on the animal species used. In men, such doses are of reasonable magnitude, which appears from this study of tetanus toxoid and from that of Edsall, Banton and Wheeler ('51) who worked with small secondary doses of diphtheria toxoid.

2. Individuals with high immunity status give less significant response, i. e., rise in titer after the secondary dose.

3. Individuals with no measurable immunity may be of two categories, previously immunized or not immunized. These inseparable categories yield widely different results, and immunization histories are necessary for efficient interpretation.

4. Inhomogeneity of the group with regard to immunizability introduces an important variable, which can rarely be determined *a priori*, except in pure inbred animal strains. This variable is most distinct after secondary stimulus.

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INBREEDING COEFFICIENTS OF THE RAMAH NAVAHO POPULATION

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INTRODUCTION

ANY discussion of inbreeding should distinguish between two senses in which the term has been used: the social, and the biological. Socially speaking, we may refer to *endogamic* mating, that is, to mating which occurs within the limits of a socially-defined category, such as a community, a clan, a caste, or a class. Biologically speaking, *inbreeding* refers to the mating of individuals with one or more common biological ancestors. Inbred individuals are offspring of genetic relatives and inbreeding is the mating of genetically related individuals.

The genetic consequences of inbreeding and endogamy may differ. Relatively small, endogamous and isolated human populations are not necessarily highly inbred. The degree of inbreeding in many natural and enduring local populations is slight compared to that characteristic of matings typical for some domestic and experimental animals.

Throughout the remainder of this paper we shall be concerned with inbreeding in the biological sense, and not, except as noted, with endogamy in the social sense.

This paper describes the types, and gives a measure of the degree, of inbreeding in the Ramah Navaho population as of September first 1948. A number of estimates of inbreeding coefficients based on various sorts of cousin marriages are available for human populations (see the summary in Neel, et al., '49). Measurements of inbreeding for relatives of all degrees, for a total human population seemingly have not been published heretofore.

INBREEDING COEFFICIENTS

Wright ('22) developed a coefficient of inbreeding that gives (for a population) the departure toward complete homozygosity from the heterozygosity expected under a system of random mating. This coefficient is a direct measure of the average effects on zygosity due to inbreeding expected from the pattern of mating in any given pedigree, population, or population segment. Wright's coefficient has the great advantage (not present in others, e. g., those of Pearl, '13, nor Krizenicky, '23) that the degree of inbreeding in an observed genealogy, however complex or irregular the pattern of mating, may be compared to that observed or expected under any regular system of inbreeding. In this way theoretical models, and the results of experiments, become useful for interpretation of human population data.

In analysis of the Ramah Navaho data, we found it convenient to use the following definition of the inbreeding coefficient, i, identical with that of Wright ($i_0 \equiv f_0$):

$$i_0 = \Sigma(1/2)^{n-1}(1 - i_A),$$

where n is the number of steps (the path from parent to offspring) in a *loop* of descent closing on an inbred individual 0, i_A is the i of a common ancestor A, and summation is over all loops terminating in 0. If A is not inbred, the coefficient is reduced to

$$i_0 = \Sigma(1/2)^{n-1}.$$

The quantity i_0 may be considered as the probability that an inbred individual with one given autosomal gene will possess two genes of common origin at the given locus. Also, i_0 may be defined as the most likely fraction of all gene pairs to consist of homozygous pairs. It is important to emphasize that the coefficient as used here is relative to the average zygosity of a random-bred population. If p is the frequency of a gene, and $(1 - p) = q$ is the frequency of its allele, the average heterozygosity of a population for the pair of alleles at equilibrium will be $2pq$. The value of p and q, of course, may vary with different gene pairs in the same population. The population effect of inbreeding on zygosity is to make the proportion of heterozygotes $< 2pq$, and thus, the proportion of homozygotes $> p^2 + q^2$.

Something of the genetic meaning of i_0 is illustrated in figure 1 where AA' represents the genotype of a common ancestor. The prob-

ability that this ancestor will pass gene A to his child is 1/2. Likewise, the probability that he will pass gene A' is 1/2. Now gene A may pass to 0 by the left side of the loop with a probability $(1/2)^3$, or by the right side with a probability $(1/2)^2$. Thus the probability that 0 will be of homozygous genotype AA is $(1/2)^5$. But gene A' may pass over the same two paths (and 0 be of genotype $A'A'$) with equal probability—thus the factor 2 in the coefficient:

$$i_0 = 2\Sigma[(1/2)^3 + (1/2)^2] = 2(1/2)^5.$$

Or, in more general terms,

$$i = 2\Sigma[(1/2)^{n_L} + (1/2)^{n_R}] = 2\Sigma(1/2)^n = \Sigma(1/2)^{n-1}$$

where n_L is the number of steps in the left side of the inbreeding loop, n_R the number in the right side, and $n = n_L + n_R$.

FIG. 1. DIAGRAMS TO ILLUSTRATE THE GENETIC BASIS OF THE INBREEDING COEFFICIENT. IN THE PEDIGREE ON THE LEFT INDIVIDUAL 0 IS INBRED; IN THE PEDIGREE ON THE RIGHT INDIVIDUAL 0′ IS NOT INBRED

The derivation and genetic significance of $i_0 = f$ is discussed in detail by Wright ('22, '51), Li ('48), and Ludwig ('44). Wright derived the coefficient of inbreeding (f) by the method of path coefficients. Bernstein's ('30) coefficient, a, is identical with f of Wright. Haldane and Moshinsky ('39) give an algebraical derivation. Malécot ('48) has shown that the general formula for f may be obtained directly from probability theory. Using matrix methods, Fisher ('49) has proposed an inbreeding statistic which is identical with $[-\log_e(1-f)]$.

In the method of Haldane and Moshinsky, the relationship of fathers and mothers (parents of the inbred individuals in question) is classified for each inbreeding loop connecting the parents and the inbred individual 0, and the value of i_0 is found by such expressions as: for full r-th cousins s times removed $i_0 = 2^{-2r-s-2}$, and for half r-th cousins s times removed $i_0 = 2^{-2r-s-3}$, the values of the i_0 being summed over all inbreeding loops that contain 0.

Calculation of the inbreeding coefficient is illustrated in figure 2 which is the pedigree of the most highly inbred sibship of the Ramah Navaho population. In this pedigree 6 different inbreeding loops connect 0 and his 6 different common ancestors. The value of i_0 for each of the 6 loops is shown in the figure, their sum totaling .0977. This

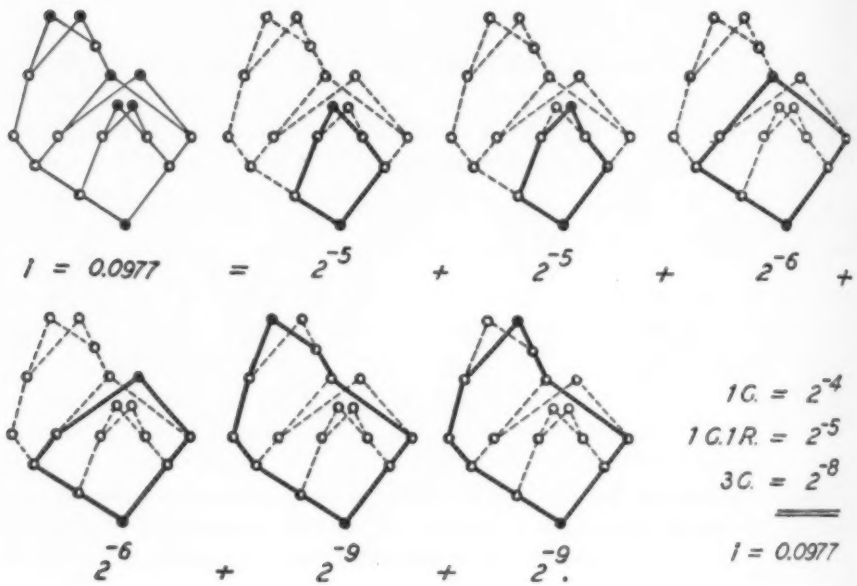

FIG. 2. DIAGRAMS TO ILLUSTRATE THE CALCULATION OF THE INBREEDING COEFFICIENT. THE PEDIGREE OF THE MOST INBRED SIBSHIP OF THE RAMAH NAVAHO POPULATION IS SHOWN ON THE UPPER LEFT. THE INBRED INDIVIDUAL AND HIS 6 COMMON ANCESTORS ARE SHOWN BY SOLID DOTS. THE 6 INBREEDING LOOPS CONNECTING THE INBRED OFFSPRING AND HIS COMMON ANCESTORS ARE SHOWN BY HEAVY LINES IN THE REMAINING 6 DIAGRAMS

value is a measure of the degree of inbreeding of individual 0. The value may be checked by classifying the relationship of 0's father to 0's mother and summing the values of i_0 for each type of relationship, following the method of Haldane and Moshinsky. The parents of 0 are related in three different ways: 1) full first cousins, $i_0 = 2^{-4}$, 2) full first cousins once removed, $i_0 = 2^{-5}$, and 3) full third cousins, $i_0 = 2^{-8}$, the sum of these values being .0977.

The above remarks on the inbreeding coefficient assume that the alleles concerned are autosomal. Roughly 95% of human gene loci are autosomal, the remaining 5% being sex-linked, holandric, and partially sex-linked, (Spuhler, '48). Haldane and Moshinsky ('39) and Wright ('51) have extended the definition of the inbreeding coefficient to cover these non-autosomal loci. Calculations of the inbreeding coefficient for sex-linked genes have been made for the Ramah population and will be presented in a later paper. The data of the present paper pertain to autosomal genes only.

THE RAMAH NAVAHO POPULATION

The Ramah Navaho are a local group of Navaho Indians residing in the vicinity of Ramah, west central New Mexico. The Navaho are an Athabascan-speaking people who have lived in the American Southwest since at least 1,000 A. D. Unlike the Anglo-American, Spanish American and Pueblo peoples of the area, the Navaho do not concentrate their population into villages. Rather, the community is composed of biological families (or more usually such families combined into extended families with matrilineal descent and matrilocal residence) widely spaced in groups of small houses or hogans. The Navaho subsistence pattern is a combination of sheep-husbandry and dry-farming agriculture. The closest Anglo-American towns are Gallup, 42 miles distant and about 11,000 in population, and Grants, 60 miles away and 3,000 in population.

Kluckhohn and Leighton ('46) give an introduction to the anthropology of the Navaho, with some emphasis on the Ramah people; Kluckhohn and Spencer ('40) provide a comprehensive bibliography of the Navaho literature up to 1940.

The group at Ramah was founded about 1820 when a few families moved into the area to hunt and farm. They were preceded there by the village-dwelling Zuni Indians, but they occupied the area before the present Spanish American, Mormon and "Texan" settlements were established. The Ramah group was reestablished soon after the Navaho returned from U. S. Army captivity at Fort Sumner, New Mexico, that is, in the decade 1870-1880.

The Ramah population is isolated geographically from the larger concentrations of Navaho in northwestern New Mexico and northeastern Arizona. The Ramah group lives in an area of about 18 by 29 miles including some 505 square miles of which about 230 are Navaho-con-

trolled. Three other Navaho communities are in the general region, one 25 miles to the north, one about 50 miles to the east, and one about 75 miles to the southeast. There has been some biological interchange between the Navaho local groups.

On September first 1948 the Ramah group totaled 614 individuals, giving a Navaho population density of around 1.22 persons per square mile. Roughly 600 non-Navaho individuals occupy the same area (mostly Anglo-Americans, Spanish Americans, and Zuni Indians) with a total population density of about 2.40 persons per square mile (see, for brief additional information, Kluckhohn and Griffith, '51).

CULTURAL FACTORS IN NAVAHO MATE SELECTION

The explicit cultural regulations on Navaho marriage are mainly defined negatively. Thus in the case of the Ramah Navaho, one may not marry:

1) a member of one's own clan,
2) a member of one's father's clan,
3) a member of a clan "linked" to one's own clan,
4) a member of a clan "linked" to one's father's clan.

The Ramah genealogies show 4 violations (out of 399 known marriages) of the first prohibition, 5 of the second. Transgression of the third and fourth regulations are more frequent but cannot be enumerated exactly because of disagreement among the Navaho themselves as to which of the clans should be considered "linked." In any case violations of these types are not as such biologically significant except perhaps at quite remote generations for which precise data are not available.

The existence of matrilineal exogamous clans among the Ramah Navaho does make for outbreeding, both because marriage with first cousins on either side is specifically forbidden (but 4 sibships in the population have been produced by first cousin matings) and because, at Ramah, all members of the same clan (with a few exceptions) can be shown to be genetic relatives. In general, it may be said that the effect of clan and clan-group exogamy is toward a wide selection of mates within the local population and toward the procurement of mates from outside communities. It tends toward forcing genes from other Navaho groups, other Indian tribes, Spanish Americans, and Anglo-Americans to be spread widely (and, in the Ramah case, thinly) in the population.

(Of the 317 fertile matings shown in the genealogies, 35 or 11.1% involve a mate from outside the Ramah population.) To some extent also, the cultural interferences with mating tend to cancel one another.

Clan membership may turn out to have other consequences for the genetic composition of this population which we are not prepared to demonstrate at present but which we hope to treat in later papers. We now call attention merely to the varying numerical composition of Ramah clans and to the fact that marriage between clans does not occur at random.

Of individuals in the genealogies whose clan membership (or non-Navaho affiliation) is definitely ascertained, 77% are included within the 4 largest clans in this area, 97% are included within the 6 largest (see Kluckhohn and Griffith, '51, p. 405 ff., for a survey of the composition as of September first 1948; data presented in that paper and in the present section overlap but also supplement one another). That is, all marriages of individuals from 15 additional clans plus those of a Yaqui Indian, a Walapai, a Laguna, a Spanish American, an Anglo-American, and 8 Chiricahua Apaches account for only 3% of the total marriages.

TABLE 1

322 Ramah Navaho marriages classified by clan membership of the spouses

Clan	B	C	D	E	F	G	H	I	Total
A	31	39	26	21	14	6	2	9	148
B	–	25	31	10	8	2	1	6	83
C		–	15	4	7	5	–	16	47
D			4	10	9	2	–	7	32
E				–	8	1	–	3	12
Total	31	64	76	45	46	16	3	41	322

Of 399 known marriages (317 of these produced sibships and are analyzed for inbreeding in this paper) almost 88% are included within marriages of members of the 5 most numerous clans with each other and with members of 4 additional clans. Table 1 shows certain preferential tendencies for clans to exchange members in ways not determined by the system of linked clan exogamy. For example, 24% of the marriages of clan A members are with clan C members, whereas 14% is expected on a random basis in proportion to numbers of available adults. Preference

is even more striking in the case of the 16 matings of clan C with clan I members. The clan I column has another interest in that it is not a "native" Ramah clan. These marriages, except for two in the founding generation, represent the securing of mates from other Navaho groups.

Additional cultural factors in mating, though not explicit regulations, are: permissible stepdaughter marriage (5 known cases in the history of this population); permissible polygyny with strong preference for sororal polygyny; easy tolerance of divorce and re-marriage and indeed minimal interference with sexual activities not constituting culturally defined "incest"; some practice of the levirate and sororate; approval of cross-generational marriages in both directions—i. e., older women also marry younger men with some frequency; tendency for repeated exchanges between biological or extended families in marriages (e. g., a man is more likely to marry the sister of his brother's wife or cousin's wife or the sister of his sister's husband).

THE DATA

Our calculations of inbreeding coefficients have been made from data summarized on a large genealogical chart showing the relationship and matings of 1118 members of the population during 8 generations (counting the initial, "founding" generation as one). The time period covered by the genealogies—as opposed to the present outbreeding population which has existed as such only since about 1870-1880—is from about 1820 to September first 1948. This genealogical chart was compiled by Clyde Kluckhohn, Katherine Spencer, and J. N. Spuhler, and drawn by Ann Tulloch. (Unfortunately, the chart is too large to reproduce with this paper; copies are on deposit in the Peabody Museum, Harvard University, and the Institute of Human Biology, University of Michigan.) The population data basic to the Ramah Navaho census and the genealogical chart were collected and worked up by members of the Ramah Project of Harvard University, especially Clyde Kluckhohn, Katherine Spencer, Janine Chappat Rosenzweig, and Nan Stoller. Individual pedigree charts (similar to that shown in figure 2) were traced by Helen Spuhler on a separate card for each inbred sibship in the population and these cards were used to calculate the coefficients for each inbred mating.

RAMAH NAVAHO MATING TYPES

Table 2 is a summary of the incidence of 62 different mating types observed in the Ramah population. Sixty-one of these mating types involve inbreeding, and of these 17 types involve matings where the parents are related in a single way, 44 types involve matings where the parents are related in two or more ways.

TABLE 2

Incidence of 62 mating types by sibship and siblings for 4 generations of the Ramah Navaho Population. See text for details.

RELATION OF MATES	p	i_0	GENERATION 5		6		7		8		Totals		% of pop. i_0
			S	I	S	I	S	I	S	I	S	I	
(1) (2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
1. F1C	4	.0625	–	–	1	6	–	–	–	–	1	6	5.076
2. HNeGA	5	.0312	–	–	1	5	–	–	–	–	1	5	2.112
3. GUHNi	5	.0312	–	–	–	–	1	7	–	–	1	7	2.956
4. F1C1R	5	.0312	3	22	–	–	–	–	–	–	3	22	9.291
5. H1C1R	6	.0156	–	–	–	–	1	9	–	–	1	9	1.900
6. F2C	6	.0156	3	16	5	32	1	1	–	–	9	49	10.347
7. DF2C1R	6	.0156	1	1	2	16	–	–	–	–	3	17	3.590
8. H2C	7	.0078	–	–	–	–	1	1	–	–	1	1	0.106
9. F2C1R	7	.0078	–	–	7	27	2	7	–	–	9	34	3.590
10. H2C1R	8	.0039	4	19	–	–	–	–	–	–	4	19	1.003
11. F2C2R	8	.0039	–	–	–	–	1	4	–	–	1	4	0.211
12. F3C	8	.0039	–	–	3	16	5*	9	–	–	8*	25	1.320
13. H2C2R	9	.0020	–	–	1	5	–	–	–	–	1	5	0.135
14. H3C	9	.0020	1	5	2	8	2	5	–	–	5	18	0.487
15. F3C1R	9	.0020	–	–	1	1	6	14	–	–	7	15	0.406
16. H3C1R	10	.0010	1	5	1	8	–	–	–	–	2	13	0.176
17. H4C	11	.0005	–	–	–	–	1	3	–	–	1	3	0.020
F1C	4												
18. F1C1R	5	.0977	–	–	–	–	1	8	–	–	1	8	10.580
F3C	8												
19. F1C	4	.0703	–	–	1	1	–	–	–	–	1	1	0.952
F2C1R	7												
F1C	4												
20. H4C	11	.0632	–	–	–	–	1	2	–	–	1	2	1.711
H4C1R	12												
21. F1C1R	5	.0352	–	–	–	–	1	1	–	–	1	1	0.476
F2C2R	8												
22. F1C1R	5	.0352	–	–	–	–	2	3	–	–	2	3	1.429
F3C	8												

* Includes one child of uncertain paternity.

TABLE 2—*Continued*

RELATION OF MATES		p	i_0	GENERATION 5		6		7		8		Totals		% of pop. i_0
				S	I	S	I	S	I	S	I	S	I	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
23.	H1C1R	6	.0352	–	–	–	–	1	1	–	–	1	1	0.476
	F2C2R	8												
	F1C1R	5												
	H1C1R	6												
24.	F2C	6	.0703	–	–	–	–	2	4	–	–	2	4	3.804
	F3C	8												
	F3C1R	9												
	DF4C	9												
	F1C1R	5												
25.	H1C1R	6	.0547	–	–	–	–	1	5	–	–	1	5	3.702
	DF3C	7												
	H1C1R	5												
26.	F2C	6	.0488	–	–	–	–	1	1	–	–	1	1	0.660
	DF4C	9												
	H1C1R	6												
27.	F2C1R	7	.0273	–	–	3	14	–	–	–	–	3	14	5.173
	F3C	8												
	H1C1R	6												
	F2C1R	7												
28.	H3C	9	.0278	–	–	2	2	2	10	–	–	4	12	4.516
	F3C1R	9												
	DH4C1R	11												
	H1C1R	6												
29.	F2C1R	7	.0264	–	–	1	5	1	3	–	–	2	8	2.859
	H3C	9												
	DH4C	10												
	H1C1R	6												
30.	F2C1R	7	.0244	–	–	1	2	–	–	–	–	1	2	0.660
	H3C1R	10												
	H1C1R	6												
31.	F3C	8	.0234	–	–	–	–	1	1	–	–	1	1	0.317
	DF3C1R	8												
32.	F2C	6	.0234	–	–	1	1	–	–	–	–	1	1	0.317
	F2C1R	7												
33.	DF2C	5	.0391	–	–	1	7	–	–	–	–	1	7	3.705
	F2C1R	7												
	F2C	6												
	H2C1R	8												
34.	DF3C1R	8	.0242	–	–	–	–	1	1	–	–	1	1	0.328
	H4C	11												
	H4C1R	12												

TABLE 2—*Continued*

RELATION OF MATES		p	i_0	GENERATION 5		6		7		8		Totals		% of pop. i_0
				S	I	S	I	S	I	S	I	S	I	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
	F2C	6												
35.	F3C	8	.0215	–	–	1	1	2	8	–	–	3	9	2.619
	F3C1R	9												
	F2C	6												
	DF3C	7												
36.	H3C	9	.0281	–	–	1	3	–	–	–	–	1	3	1.141
	F3C1R	9												
	H4C	11												
	H4C1R	12												
	F2C	6												
37.	H2C	7	.0254	–	–	1	4	–	–	–	–	1	4	1.375
	H3C	9												
	F2C	6												
	H2C	7												
38.	H3C	9	.0283	–	–	–	–	–	–	1	2	1	2	0.766
	F3C1R	9												
	FC4	10												
39.	H2C	7	.0117	–	–	–	–	2	7	–	–	2	7	1.109
	F3C	8												
40.	H2C	7	.0156	–	–	–	–	1	1	–	–	1	1	0.211
	DF3C	7												
	H2C	7												
	F3C	8												
	F3C1R	9												
41.	H3C1R	10	.0166	–	–	–	–	–	–	1	3	1	3	0.674
	F4C	10												
	F4C1R	11												
	H4C	11												
	H2C	7												
42.	F2C1R	7	.0186	–	–	–	–	1	1	–	–	1	1	0.252
	H3C	9												
	F4C	10												
	H2C	7												
43.	F3C1R	9	.0105	–	–	–	–	1	1	–	–	1	1	0.142
	H4C	11												
	H4C1R	12												
44.	F2C1R	7	.0117	–	–	2	6	–	–	–	–	2	6	0.950
	F3C	8												
	F2C1R	7												
45.	F3C	8	.0137	–	–	1	3	–	–	–	–	1	3	0.556
	H3C	9												
	F2C1R	7												
46.	H3C	9	.0107	–	–	1	1	–	–	–	–	1	1	0.145
	H3C1R	10												

TABLE 2—*Continued*

RELATION OF MATES	p	i_0	GENERATION 5		6		7		8		Totals		% of pop. i_0
(1) (2)	(3)	(4)	S (5)	I (6)	S (7)	I (8)	S (9)	I (10)	S (11)	I (12)	S (13)	I (14)	(15)
47. F2C1R F3C1R	7 9	.0098	–	–	1	3	–	–	–	–	1	3	0.398
48. F2C1R H4C	7 11	.0083	–	–	2	7	–	–	–	–	2	7	0.786
F2C2R 49. H2C1R F3C1R H4C1R	8 8 9 12	.0100	–	–	–	–	–	–	1	3	1	3	0.406
50. H2C1R F3C1R	8 9	.0059	–	–	–	–	7	19	–	–	7	19	1.517
51. H2C1R H3C1R	8 10	.0049	–	–	–	–	1	2	–	–	1	2	0.133
52. F3C H4C	8 11	.0044	–	–	–	–	1	1	–	–	1	1	0.060
53. F3C H4C1R	8 12	.0042	–	–	–	–	1	2	–	–	1	2	0.114
54. H3C H3C1R	9 10	.0029	–	–	1	1	–	–	–	–	1	1	0.039
55. H3C F4C	9 10	.0029	–	–	–	–	2	5	–	–	2	5	0.196
56. F3C1R H4C1R	9 12	.0022	–	–	–	–	1	2	–	–	1	2	0.060
57. H3C1R H4C	10 11	.0015	–	–	1	6	–	–	–	–	1	6	0.122
H2C 58. DF3C1R H3C1R	7 8 10	.0127	–	–	–	–	1	1	–	–	1	1	0.172
H2C 59. H3C F4C	7 9 10	.0107	–	–	–	–	1	1	–	–	1	1	0.145
H2C 60. F3C H3C F4C	7 8 9 10	.0146	–	–	–	–	–	–	2	3	2	3	0.593
H1C1R 61. F2C F3C1R F4C	6 6 9 10	.0342	–	–	–	–	–	–	1	2	1	2	0.926
Totals, inbred matings			13	68	46	191	58	151	6	13	123	423	100.000
62. "Unrelated"	0		47	204	68	223	39	68	1	1	155	496	
Totals, all matings			60	272	114	414	97	219	7	14	278	919	

In column 1 of table 2 a serial number is assigned to the various mating types. Column 2 gives the "relation of mates" for each type. The following abbreviations are used in this column:

A — Aunt	Ni — Niece
C — Cousin	R — Removed
D — Double	U — Uncle
F — Full	1 — First (or, preceding R, Once)
G — Great	2 — Second (or, preceding R, Twice)
H — Half	3 — Third
Ne — Nephew	4 — Fourth

For example, "DH4C1R" means "*D*ouble *H*alf *F*ourth *C*ousins *O*nce *R*emoved."

Column 3 gives the power (p) of the exponent fixing the contribution of each *type of parental relationship* to the inbreeding coefficient. For example, F1C (Full First Cousins) contribute $(1/2)^4$ to the coefficient (as explained above).

Column 4 gives the contribution for autosomal loci of each *type of mating* to the coefficient. This is the sum of (p) over each of the various sorts of relationship (or, over each inbreeding loop) between the mates involved in each mating. For example, in mating type 18, $i = 0.0977$, which is the sum of $(1/2)^4 + (1/2)^5 + (1/2)^8$.

Columns (5-12) in table 2 give the incidence of inbreeding by sibships (S) and by individuals (I) in generations 5, 6, 7, and 8 of the Ramah population together with the totals (columns 13-14) for each mating type, and the proportion (column 15) which each inbred mating type contributes to the population mean inbreeding coefficient.

Table 2, then, gives the distribution of all inbred individuals by mating type and generation. There are 123 inbred sibships containing 423 individuals. No inbreeding is known for generations 1 through 4 of the population, although the genealogies of the second, third, and fourth generations are established in fine detail. There are a total of 38(+) sibships with 199 offspring in generations 1-4. The number of sibships involved in the case of the 14 members of generation 1 is not exactly established.

Included in generations 5-8 are 496 "unrelated" individuals from 155 "outbred" sibships. There are, thus, a total of 278 matings of 62 different types in generations 5-8. These matings produced a total of 919 offspring.

TABLE 3

Inbreeding Coefficients of the Ramah Navaho Population

Generation	Number of Sibships	Number of Sibs	Number of Outbred Matings	Number of Outbred Sibs	Size of Outbred Sibships	Number of Inbred Matings	Number of Inbred Sibs	Size of Inbred Sibships	Range of Inbreeding Coefficient of Inbred Sibs	Mean Inbreeding Coefficient of Inbred Sibs	Mean Inbreeding Coefficient of Total Sibs
1	?	14	?	?	?	?	?	?	—	—	—
2	8	27	8	27	3.38	0	0	0	0	0	0
3	8	35	8	35	4.38	0	0	0	0	0	0
4	22	123	22	123	5.59	0	0	0	0	0	0
5	60	272	47	204	4.34	13	68	5.23	.0010-.0312	.0153	.0038
6	114	414	68	223	3.28	46	191	4.15	.0013-.0703	.0157	.0073
7	97	219	39	68	1.74	58	151	2.60	.0010-.0977	.0205	.0141
8	7	14	1	1	1.00	6	13	2.17	.0078-.0283	.0191	.0178
Inbred Sub-totals	–	–	–	–	–	123	423	3.44	.0010-.0977	.0175	—
Population Totals	316	1118	193	681	3.53	123	423	3.44	.0010-.0977	.0080	.0066

Table 3 is a summary by generation of the inbreeding coefficients of the Ramah population, with information on all generations since the founding of the population.

Some particular value of the inbreeding coefficient may have at least 4 different referents (Ludwig, '44; Wright, '51). It may refer to: (a) an individual, (b) the offspring of a given mating, i. e., a sibship, (c) a generation, or (d) a breeding population. Table 2 gives the raw data for determination of the first three of these sorts of referents. Table 3 summarizes this data in different form and gives information on outbred matings of generations 1-8.

Information is presented on 316 matings which produced 1118 offspring in 8 generations. 193 of these matings were outbred and produced 681 offspring. The remaining 123 matings were inbred and produced 423 offspring.

The range of the inbreeding coefficient for individuals (or full sibs) is .0010 to .0977. The mean coefficient for all *inbred* individuals for generations 5 through 8 is .0175. The mean coefficient for the population (generations 5 through 8 only) is .0080. The mean coefficient for the entire population since the foundation (generations 1 through 8) is .0066.

GRAPHICAL REPRESENTATION OF THE POPULATION

Homogeneous coordinates may be used to represent a Mendelian population (de Finetti, '27, Haldane and Moshinsky, '39). The frequencies of n genotypes which occupy a single autosomal locus may be represented by a point within a regular simplex in $(n-1)$ dimensional space where the perpendiculars of its n bounding planes are coordinates whose sum is unity. Thus the population frequencies of the three genotypes $(x\,AA + y\,Aa + z\,aa = 1)$ formed by a single pair of autosomal alleles, A and a, may be represented (fig. 3) by a point P in an equilateral triangle XYZ, where x, y, z are the perpendiculars from P on YZ, XZ, and XY respectively. If we let the gene frequencies of $A = p$, and of $a = (1-p) = q$, then $p = x - 1/2y$, and the points representing a population with a given gene ratio $(p:q)$ lie on the straight line PQ, where Q is the projection of P on XZ. The equations for $QZ = p$ are $x - 1/2y = p$, and $2qx + (q-p)y - 2pz = 0$.

Under a system of random mating, $x = p^2$, $y = 2pq$, and $z = q^2$, and the points generated by a parabola $y^2 - 4xz = 0$ (with vertex at the mid-point of the altitude of the triangle and with tangents to XY and

YZ at X and Z respectively) represent the genotype frequencies for autosomal single alleles in all possible ideally large random-mating populations.

Under a regular system of inbreeding the frequency of heterozygotes is reduced by a factor $(1 - i)$ where i is, of course, the inbreeding coefficient. Thus the frequencies of the three genotypes in regularly-inbred populations are $x = p^2 + ipq$, $y = 2(1 - i)pq$, and $z = q^2 + ipq$.

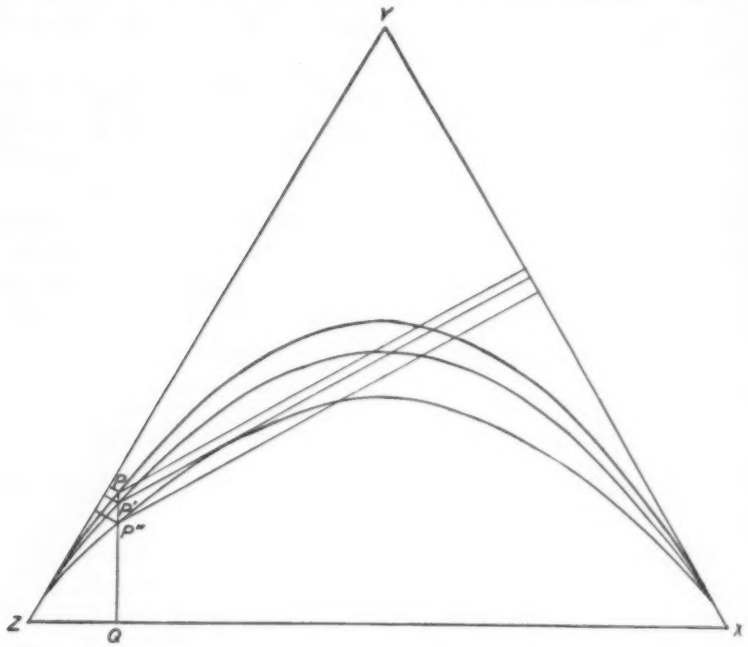

FIG. 3. GRAPHICAL REPRESENTATION OF GENE FREQUENCIES AND GENOTYPE FREQUENCIES FOR THREE VALUES OF THE MEAN INBREEDING COEFFICIENT OF A POPULATION. THE PARABOLAS ARE DEFINED IN THE TEXT AND THE THREE POINTS P, P', P'' ARE DEFINED IN TABLE 4

Three parabolas are shown in figure 3. The uppermost parabola represents the locus of points whose perpendicular coordinates measure the genotype frequencies for autosomal single alleles in a random-mated population. The middle parabola represents the locus of such points for the ideal case of a population practicing a regular system of inbreeding of such a degree that $i = .0977$. As shown above, this value is the maximum inbreeding coefficient observed for an individual Ramah

Navaho. The lowermost parabola represents the locus of points for a population following a regular system of full brother-sister mating for one generation.

The parabola representing the locus of points for a system of inbreeding where $i = .0080$ (the mean for generations 5 through 8 of the Ramah group) would lie below but very close to the parabola for a system of random mating. It follows that the distribution of autosomal genotype frequencies in the Ramah population would not be expected to show marked deviations from the proportion of heterozygotes expected under a system of random mating. We can illustrate this fact by considering the genotype frequencies for some particular gene frequency. Since the B gene (a^B) of the ABO blood group system is absent in the Ramah population, we may treat the $A(A)$ and $O(a)$ genes as a pair of single autosomal alleles. (The distribution of the MN blood types at Ramah will be considered in the following section.) The population frequencies of the AO genes based on a pooled sample of 458 individuals (Boyd and Boyd, '49; Mourant, '50) are $p = \bar{A} = .126$ and $r = \bar{a} = .874$ ($q = \bar{a}^B = 0$).

TABLE 4

Genotype frequencies for 4 ideal systems of mating and the observed gene frequencies of ABO blood group genes of A and a in the Ramah Navaho population

Mating system	Inbreeding Coefficient, i_0	Group A		Group O	Total
		$x\,AA$	$y\,Aa$	$z\,aa$	
P	0	.016	.220	.764	1.000
P_{RN}	0.0066	.017	.218	.765	1.000
P'	0.0977	.027	.199	.774	1.000
P''	0.25	.043	.165	.792	1.000

The segment of the base of the triangle QZ represents the gene frequency p and the segment QX represents the gene frequency $(1 - p) = r$. The genotype frequencies in the population are determined jointly by these gene frequencies *and* the system of mating. We will consider four such systems. Three different mating systems are shown in figure 3 by points P, P' and P''. The fourth mating system is shown only in table 4 by point P_{RN} and indicates the appropriate genotype frequencies for a system of mating where the mean inbreeding coefficient is $i = .0066$. Inspection of the values in the graph and in the table indicates that the

observed degree of inbreeding in the Ramah population would not be expected to bring about large deviations from the genotypical proportions theoretically appropriate for a system of random mating in the population.

INDIRECT ESTIMATE OF THE INBREEDING COEFFICIENT OF THE RAMAH POPULATION

Now that we have direct estimates of the inbreeding coefficient of the Ramah Navaho population, it is possible to compare the results with an estimate obtained by an indirect method. Haldane ('38) has shown that departures in the amount of heterozygosity from that expected under random mating can be interpreted to give evidence for the mating system in natural populations.

Consider a pair of autosomal alleles, such as the genes responsible for the *MN* blood types in man, where heterozygotes are distinguishable by phenotypical inspection. We will represent the three phenotypes by *M*, *MN*, and *N*, and their respective genotypes by *MM*, *Mm*, and *mm*. Let the observed phenotypical frequencies in the population be

$$a\,M + b\,MN + c\,N = n.$$

If the population was reproduced by random mating (with regard to the alleles *M* and *m*) and the gametes from the previous generation are represented by the proportion $u\,M : 1\,m$, the expected distribution of genotypes would be

$$nu^2/(u+1)^2\,MM : 2nu/(u+1)^2\,Mm : n/(u+1)^2\,mm.$$

The logarithm of the likelihood of the observation is

$$L = (2a+b)\log u - 2n\log(u+1).$$

Thus

$$dL/du = (2a+b)/u - 2n/(u+1) = 0,$$

and

$$u = (2a+b)/(b+2c) \pm \sqrt{2n(2a+b)/(b+c)^2}.$$

If this value of u is applied to the expected distribution of genotypes given above, the expected and observed numbers for each phenotype may be compared. A χ^2 test is appropriate.

If the differences between expected and observed values are too large to be consistent with a hypothesis of random mating, and the departure

is in the direction of an excess of homozygotes, inbreeding is one of several possible explanatory factors. (In the case of the *MN* blood groups, probably we can safely exclude the possible explanatory factor of assortative mating.)

Bernstein ('30) found that expected ratios of the genotypes in an inbred population (with inbreeding coefficient i) are

$$(u^2 + iu)MM : 2(1 - i)u\,Mm : (iu + 1)mm.$$

Since the genotypes can be distinguished by serological tests, if we let, as above, the observed frequencies of phenotypes be

$$a\,M + b\,MN + c\,N = n,$$

then

$$u = (2a + b)/(b + 2c),$$

and

$$i = (4ac - b^2)/(2a + b)(b + 2c).$$

The observed distribution of the *MN* blood types in a sample of 458 Ramah Navaho (Boyd and Boyd, '49; Mourant, '50) is

$$380\,M + 74\,MN + 4\,N = 458$$

$u = 10.1707$, the expected distribution is

$$379.67\,M + 74.66\,MN + 3.67\,N = 458.00,$$

$\chi^2_1 = 0.0358$, and $0.8 < P < 0.9$.

Although the departure of the observed distribution from the expected values is in the direction of an increase in the proportion of homozygotes, that is, in the direction expected for an inbred population, the observed values are fully consistent with the hypothesis of random mating. But, as shown in the preceding section, the observed mean value of the inbreeding coefficient for the Ramah population is sufficiently small, and has been in effect for a sufficiently short period of time, that large deviations from the theoretical proportions appropriate for random mating are not to be expected. With this in mind, and noting that gene m is relatively rare in the population and that estimates of its frequency are subject to considerable fluctuation in small samples, it remains of interest to solve for the inbreeding coefficient. We find $i = .0088$. This indirectly obtained value is remarkably close to the directly obtained value .0080 for the mean inbreeding coefficient for all sibs in generations 5 through 8.

DISCUSSION

In previously published estimates of inbreeding coefficients in human populations, samples of matings have been classified into inbred *versus* outbred and a coefficient of inbreeding estimated from the ratio of first cousin, second cousin, and other consanguineous matings (usually not beyond third cousins once removed) to "unrelated" matings. The size of the sibship produced by the two sorts of mating is not entered into such estimates. We have 123 cases of 61 different sorts of inbred matings out of a total of 316 matings (including the sixty-second sort, "unrelated") for generations 5 through 8. i_0 for inbred matings is $(1.9847/123) = .0161$ and for total matings i_0 is $(1.9847/316) = .0063$. This estimate is lower than the estimate we obtained for total individuals in generations 5-8 ($i_0 = .0080$) because our inbred families of generations 5-8 have more offspring than the outbred families.[1]

Caution is required for the proper interpretation of our population mean coefficient of inbreeding. First, the value should be regarded as a minimum estimate of the true value of the coefficient. As a result of extensive field work over a period of 16 years, the Ramah genealogies are remarkably complete for generations 2-8. There are some unknowns in the founding generation. If any of the 14 founders are themselves *inbred,* the mean values of the population coefficient would be slightly larger. However, since no inbreeding was practiced in generations 2-4 (where genealogical information is "complete") this possible source of error would not greatly modify the total population estimates (on the assumption, of course, that there are no undetected relationships among the founders).

[1] The crude data suggest that inbreeding in the Ramah population has not reduced fertility of inbred individuals, although when the data for all generations are pooled the average size of outbred sibships is 3.53 persons, and for inbred sibships, 3.44 persons. However, when the crude data are compared by generation, inbred sibships average consistently larger than outbred, the respective means for generations 5-8 being 3.44 as against 3.20. The larger sibships in the earlier generations (mean of generations 2-4 = 4.45) make a relatively large contribution to the population mean. Of course such crude data may be highly misleading. Many of the families of generation 7 and 8 are incomplete. In a later paper on the demography of the Ramah group we will examine the size of inbred and outbred sibships in terms of exposure to pregnancy. For the present we may conclude that inbreeding in the present group has not been accompanied by a marked decrease in fertility.

If there are undetected *biological relationships among* the 14 founders, the mean values for subsequent generations could be increased considerably. However, the known relationships among the founders is of the sort which might be expected on the basis of general knowledge of Navaho behavior. With due regard to the unknowns in the case, our opinion is that the estimated values for the population, while somewhat low, are not greatly low, perhaps not more than 10%.

Another difficulty in arriving at an estimate of the true value of the inbreeding coefficient is the problem of determining true population size. Although the Ramah group is relatively isolated (see above) and relatively self-contained, there are a few individuals regarding whose membership in the population an arbitrary judgment must be made. Actually we made an independent classification of the individuals represented in the census data of the Ramah area. These data include information of residential history, travel, participation in other Navaho communities, and work in extra-Navaho contexts. The census included information on a number of individuals who have a marginal participation (in both biological and socio-cultural terms) in the Ramah population. Our result differed only with regard to a single outbred family with 9 children. JNS classed the entire family in the population while CK put the father in, and the remainder of the family out of the population. For the present calculations, all 11 individuals have been included in the population. If our criteria for membership were made extremely broad, the population size, as of September first 1948, would be increased by some 20 individuals, and the size over all generations reported here would be larger by about 70 individuals. Use of the larger population sizes would result in a slight reduction of the population estimates of the mean value of the inbreeding coefficients, but not a marked reduction because some of these 70 individuals are themselves inbred.

In previously published estimates, data have not been available on the more remote relationships. It is of interest to compare our results based on "full" specification with those obtained when the coefficient is estimated from various degrees of incomplete specification. We will examine three cases: 1) estimates from the incidence of first cousin (1C) matings; 2) estimates based on the incidence of first and second cousin (1C + 2C) matings; and 3) estimates based (as in the Hiroshima and Kure data reported in Neel, et al., '49) on the incidence of matings involving first cousins, first cousins once removed, second cousins, second cousins once removed, third cousins, and third cousins once removed.

Case	Based on Relationships	Estimate of i_0	Percentage of total $i_0 = (.0080)$ contributed by these matings
1.	F1C	.0008	10.0
2.	F1C+F2C	.0020	25.0
3.	F1C+F1C1R+F2C1R+F3C+F3C1R	.0034	42.5

In the case of the Ramah population, our estimate for the generations reported here would have neglected about 57% of the known inbreeding had we restricted our study 1) to degrees of relationship equal to or greater than third cousins, and 2) to specification of a single (closest) type of relationship for each inbred mating.

This datum is not of direct use in estimating the amount of underestimation of the inbreeding coefficient in other studies. The datum is closely influenced by factors specific for the Ramah community, for example, the effective size of the local breeding population, and the local Navaho cultural patterns of mate selection. However, the datum is suggestive for the interpretation of reported values for the inbreeding coefficient. We might guess, for instance, that the estimate by Neel et al. ('49) and by Schull ('53) in the Japanese case—where marriages of first cousins are culturally permissive and actually performed fairly often—would be closer to the true value, than the estimate of Haldane and Moshinsky ('39) based on data of Orel ('32) in the case of Catholic marriages in the archdiocese of Vienna where marriage of first cousins is by special dispensation and not a culturally preferred type of mating. In these studies, the specification of relationships was restricted to degrees equal to or greater than third cousins and multiple relationships were not specified.

SUMMARY

Inbreeding coefficients are calculated for 316 matings which produced 1118 offspring during 7 generations of the Ramah population. Of the 316 sibships, 123 are inbred. The range of the inbreeding coefficient for individuals is .0010-.0977, the mean for inbred siblings is .0175, and the mean for the later generations 4 through 8 is .0080, and the mean for the total population, generations 1 through 8, is .0066. These values are minimum estimates for the population.

Coefficients of the order observed for the Ramah Navaho, while about two times those found for Japan and 4 times those reported for Europe, are small compared to the estimate for the Dunker isolates in the United

States and compared to such regular systems of inbreeding as full first cousin mating.

Although the small Ramah Navaho population is not highly inbred, mating of the more remote relatives makes a comparatively large contribution to the mean value of the inbreeding coefficient.

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STUDIES ON THE VARIABILITY OF HUMAN URINARY EXCRETION PATTERNS

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INTRODUCTION

As our knowledge of biochemical genetics increases, the question of the genetic control of human differences comes more to the forefront. Some of the "inborn errors of metabolism," such as alcaptonuria and phenylketonuria, have been recognized for many years. More recently attention has been focused on the differences which occur between people whose various metabolic processes fall within the normal range of variation. While some of these differences are undoubtedly a function of the environment of the individuals, evidence is accumulating which indicates that many of the observed differences are of a more fundamental nature and that some of them may have their origin in genetic differences between the individuals.

Many experiments, although not designed to demonstrate these genetic relationships, show the marked individuality which exists for many body constituents. McGavack and Drekter ('45) found that thyrotoxic patients show changes in blood cholesterol after treatment with thiouracil, but each person maintained his relative position with respect to the other patients. Groen and coworkers ('52) subjected 60 individuals to diets containing from one to 900 mg cholesterol/day and were able to change the blood levels only slightly. They found that each person reacted in his own characteristic way to the different diets. They suggested that the cause of these individual peculiarities may be of a hereditary nature.

[1] This study was supported in part by a grant from McGregor Fund of Detroit, Michigan.

Serum alkaline phosphatase in cattle has been shown to vary widely among individuals although remaining relatively constant for a particular animal (Crookshank, et al., '52); Wagner and Poindexter ('52) reported a constitutional individuality in the level of cholesterol-esterifying activity in human serum. Kajiro and coworkers ('52) have reported on a constitutional anomaly in which there is a lack of the enzyme catalase in the blood and certain tissues. Wilkins and Carlson ('52), studying the qualitative differences in neutral 17-ketosteroids excretion in normal subjects, found that although the total amounts excreted in the urine might vary with environmental changes, the qualitative pattern of each person was highly characteristic for the individual.

Among the more interesting recent studies in biochemical genetics have been the demonstrations that genetically controlled variations in human hemoglobin exist. Itano ('53) has summarized some of the properties of the different hemoglobins along with their relationships to certain blood conditions.

Of the various anomalies of amino acid excretion, cystinuria has perhaps been most adequately studied. Dent and Harris ('51) have summarized the characteristics of the different types of cystinuria, emphasizing the genetic relationships. The increased excretion by some people of the recently discovered amino acid β-aminoisobutyric acid is reported to have a genetic basis (Crumpler, et al., '51). Fink, Henderson, and Fink ('51) also found the excretion of this amino acid to vary widely from person to person. With the advent of paper chromatography, a number of studies of individuality in urinary excretion patterns have been made (e. g. Williams, '51; Berry, Cain, and Rogers, '51; Sutton, '51). An interpretation of these results in terms of the genetic makeup of the individual has recently been made (Berry, '53).

The results reported here are from a study of urinary excretion products of 32 individuals (16 sib pairs). The data were analyzed in such a way as to answer the following questions: (1) Does an individual on repeated sampling tend to show a characteristic level of excretion of the particular substances measured? (2) If so, does the individual tend to resemble his sibling in this respect more than would be expected by chance? (3) Can individuals be characterized by excretion *patterns* as opposed to excretions of particular substances? The affirmative answers which have been obtained should help form a sound basis for further study in the field of human biochemical genetics.

EXPERIMENTAL

The subjects of this study were 32 patients of the Coldwater State Home and Training School, Coldwater, Michigan, and consisted of 16 pairs of siblings. Two of the sib pairs, on the basis of their serological and morphological types, were probably identical twins (kindreds 08 and 13). All of the patients were classified as mentally deficient with no known organic defect. Both members of kindred 29 were blind or nearly blind, however. There were 13 males and 19 females whose ages varied from 7 to 33 and whose IQ's varied from 28 to 83. The sexes are indicated in table 1.

Three first morning urine samples were collected from each of the patients on alternate days. All samples were collected within a three-week period. The samples were frozen soon after collection and were stored in that state except when necessary to remove aliquots for analysis.

Creatinine determinations were done by the method of Bonsnes and Taussky ('45) and inorganic phosphorus by the method of Fiske and SubbaRow ('25). All other substances were measured by paper chromatographic techniques using conditions previously specified (Sutton, '51) except that aliquots of urine containing 40 μg creatinine were used for the bromcresol green (BCG) chromatograms. One alteration in the procedure was the use of reflectance measurements to quantify those amino acids for which ninhydrin had been used for color development. For this purpose a Beckman model B spectrophotometer equipped with an integrating sphere reflectance attachment with beam expanding lens was used. The filter paper containing the ninhydrin-developed amino acid was placed in the instrument so that the light beam (550 mμ) was centered on the point of maximum color density. Quantitative values for the unknowns were obtained by comparing their percentage reflectance with a standard curve based on the reflectances of known quantities treated in the same manner. Alanine was used as the standard for glutamine, ethanolamine and β-aminoisobutyric acid, and the values for these substances are expressed as mg alanine. This procedure requires considerably less time than most other methods in the literature and is capable of the same accuracy.

The substances designated "BCG acid .28," "BCG acid .30," and "BCG basic .32" refer to spots of unknown composition which appear on bromcresol green chromatograms resolved in butanol-acetic acid-water

TABLE 1

TABLE 1

Measurements of Urinary Constituents

Subject	Sex	Age yr	Age mo	IQ	pH			Spec. Grav. (−1, x10³)			Optical Dens. (x 10²)			Creatinine (Cr) mg/ml			Phosphorus mg P/ml		
					A*	B	C	A	B	C	A	B	C	A	B	C	A	B	C
22 33	F	26	1	63	6.25	5.52	6.25	31	25	12	048	052	101	1.70	1.70	0.78	1.49	1.22	0.42
22 34	F	24	2	61	5.58	5.49	5.77	19	23	27	073	367	052	1.54	2.12	2.68	1.12	1.68	1.65
14 25	M	11	5	60	6.49	6.21	6.18	15	10	16	312	213	217	0.80	0.70	0.59	0.60	0.40	0.73
14 24	M	12	9	59	7.36	6.23	6.98	16	19	10	177	258	485	0.64	0.65	0.40	0.48	0.70	0.43
23 35	M	27	3	39	5.78	5.74	5.72	18	24	22	066	035	043	1.22	1.82	1.52	0.72	1.60	1.07
23 36	M	17	8	54	6.02	5.43	6.43	18	26	22	053	051	077	1.00	2.13	1.25	0.58	1.66	0.76
24 37	M	7	6	58	6.11	5.92	6.17	20	26	04	103	204	088	0.66	1.04	0.28	0.93	1.08	0.26
24 38	F	14	11	58	5.54	5.56	5.73	15	21	18	032	056	067	1.35	1.68	1.07	0.91	1.11	0.84
25 39	M	22	2	53	5.46	5.76	5.86	29	32	23	102	097	034	1.98	3.47	2.08	1.91	2.37	1.46
25 40	M	16	8	61	6.41	6.06	5.68	27	29	30	332	122	077	1.75	1.96	1.48	0.95	1.28	1.42
12 21	F	31	6	53	5.66	6.82	5.43	18	17	15	091	302	117	1.56	0.99	0.90	0.70	0.69	0.66
12 20	F	25	3	39	7.12	6.42	6.69	21	18	21	193	123	152	1.68	1.19	1.32	1.17	1.16	0.87
26 41	M	14	9	28	6.15	5.58	5.98	15	28	27	082	038	170	0.64	1.62	0.95	0.52	0.77	0.85
26 42	M	13	4	28	6.08	5.86	5.83	23	17	22	340	276	156	0.80	0.85	0.90	0.73	0.58	0.75
09 15	M	17	8	62	7.48	6.07	6.63	05	18	19	048	027	034	0.55	1.59	1.30	0.10	0.84	0.55
09 14	M	12	6	83	6.86	6.93	6.43	12	10	19	038	054	145	0.61	0.72	0.83	0.25	0.23	0.71
27 43	F	10	0	69	5.42	5.05	5.74	15	29	29	044	047	083	0.58	1.04	1.29	0.57	0.85	1.77
27 44	F	12	1	59	7.30	7.44	6.58	14	22	18	136	156	125	0.67	0.66	0.79	0.31	0.50	0.74
11 19	F	21	4	48	6.53	6.36	6.13	15	19	27	146	202	121	0.93	1.23	1.83	0.61	0.97	1.55
11 18	M	18	6	64	5.70	6.53	5.63	26	25	26	138	076	112	1.82	1.78	1.68	1.65	1.54	1.29
07 11	F	11	9	54	6.32	6.49	5.83	25	33	31	344	072	142	1.28	1.67	1.53	1.10	1.71	2.33
07 10	F	18	5	64	6.04	6.02	5.94	28	30	30	092	102	106	1.50	1.90	2.69	1.61	1.92	2.18
28 45	M	7	4	56	5.93	6.43	6.22	24	18	26	057	113	114	1.08	0.79	1.27	0.65	0.58	1.11
28 46	F	13	5	61	6.58	6.22	6.56	23	25	23	065	143	102	1.15	1.93	1.24	0.77	1.08	0.72
29 47	F	12	11	63	5.72	8.82	6.76	28	23	25	042	093	075	1.99	1.20	1.19	1.55	0.65	0.88
29 48	F	11	1	63	7.17	7.05	6.42	21	20	23	112	087	052	0.90	0.90	1.14	0.55	0.63	1.06
08 13	F	7	5	76	7.12	6.18	6.26	11	28	20	315	162	056	0.53	0.52	0.96	0.66	0.80	0.80
08 12	F	7	5	76	7.43	6.22	6.07	17	05	18	067	081	097	0.42	0.73	0.84	0.17	0.73	0.98
13 22	F	10	6	59	5.91	7.78	6.12	16	11	15	288	590	232	0.59	0.45	0.70	0.43	0.33	0.73
13 23	F	10	6	71	8.23	6.32	6.43	16	17	21	301	287	258	0.78	0.50	0.76	0.63	0.65	0.94
10 16	F	33	2	68	5.73	6.22	5.92	12	07	08	042	078	091	1.23	0.44	0.44	1.06	0.35	0.27
10 17	F	27	9	75	6.18	7.53	5.53	18	14	15	049	033	046	1.19	1.12	1.35	0.87	0.78	0.85

* A, B and C refer to the three samples for each individual.

TABLE 1 (Continued)

Subject		Uric acid mg/ml			Histidine·HCl mg/ml			Alanine μg/mg Cr			β-Aminoisobutyric acid μg/mg Cr			Glutamic acid μg/mg Cr			Glutamine μg/mg Cr			Ethanolamine μg/mg Cr		
		A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
22	33	0.35	0.15	0.12	0.12	0.12	0.05	17	07	06	06	00	00	02	02	02	17	11	09	00	00	00
22	34	0.20	0.30	0.12	0.12	0.10	0.12	11	11	11	00	00	00	00	00	00	13	13	13	00	00	00
14	25	0.20	0.35	0.30	0.02	0.05	0.10	27	09	19	15	NV	15	08	00	00	32	15	24	06	00	06
14	24	0.20	0.05	0.20	0.10	0.10	0.05	20	18	15	11	15	NV	10	00	05	29	25	21	00	08	00
23	35	0.20	0.30	0.25	0.10	0.12	0.10	06	11	10	00	06	00	00	00	00	12	16	11	02	04	00
23	36	0.25	0.40	0.70	0.10	0.10	0.12	12	11	15	00	00	00	00	00	00	12	11	16	00	00	00
24	37	0.20	0.50	0.03	0.12	0.17	0.01	45	61	30	05	NV	00	00	00	05	48	57	23	11	16	06
24	38	0.15	0.40	0.20	0.12	0.12	0.10	11	11	19	00	03	06	00	00	00	13	13	25	00	02	05
25	39	0.30	0.50	0.25	0.12	0.12	0.10	14	11	13	00	00	00	00	00	00	14	13	16	04	00	00
25	40	0.15	0.40	0.40	0.12	0.15	0.15	36	18	20	00	00	00	NV	NV	00	40	25	23	00	00	02
12	21	0.40	0.25	0.30	0.12	0.12	0.10	19	25	27	07	08	NV	00	00	00	21	18	32	00	06	06
12	20	0.60	0.40	0.50	0.12	0.12	0.15	11	18	23	08	08	NV	10	02	00	19	27	32	00	06	06
26	41	0.25	0.40	0.15	0.15	0.15	0.20	38	27	68	04	00	10	00	00	00	38	24	68	03	00	08
26	42	0.25	0.25	0.08	0.15	0.15	0.15	57	29	38	00	06	00	00	00	00	43	24	32	02	02	02
09	15	0.07	0.12	0.25	0.10	0.12	0.12	19	19	17	19	13	15	11	07	08	19	14	21	00	00	00
09	14	0.20	0.25	0.22	0.10	0.06	0.10	32	15	20	14	12	13	00	05	07	29	18	40	05	00	06
27	43	0.15	0.15	0.50	0.08	0.10	0.15	17	27	17	04	NV	05	00	00	00	21	32	29	03	04	03
27	44	0.15	0.25	0.40	0.10	0.15	0.10	30	38	29	06	10	04	07	10	06	40	51	36	04	00	00
11	19	0.25	0.80	0.60	0.12	0.15	0.15	25	24	21	10	NV	06	05	02	01	32	34	27	06	05	04
11	18	0.50	0.55	0.50	0.12	0.12	0.12	13	13	13	00	13	10	00	05	00	19	20	24	04	06	06
07	11	0.80	1.10	0.60	0.17	0.40	0.40	36	68	34	07	NV	03	00	05	00	48	86	68	04	04	00
07	10	0.80	0.60	1.20	0.15	0.15	0.12	20	32	13	07	NV	02	05	02	02	29	38	19	00	00	00
28	45	0.35	0.15	0.30	0.15	0.10	0.20	40	25	48	00	00	13	00	05	NV	54	45	64	09	04	09
28	46	0.15	0.30	0.15	0.20	0.15	0.15	43	17	24	08	00	08	00	00	00	57	25	38	09	02	02
29	47	0.40	0.20	0.10	0.15	0.15	0.15	23	36	24	00	05	00	00	09	NV	24	30	30	00	00	00
29	48	0.20	0.20	0.20	0.10	0.10	0.15	34	23	29	11	06	10	NV	05	06	36	23	29	00	00	00
08	13	0.50	0.18	0.35	0.05	0.10	0.08	13	30	14	08	17	07	08	05	04	13	32	20	00	09	00
08	12	0.10	0.12	0.25	0.02	0.10	0.08	09	19	11	05	NV	07	04	00	04	12	21	21	00	06	04
13	22	0.15	0.03	0.20	0.04	0.05	0.06	24	27	19	11	11	09	00	11	00	29	32	36	08	00	09
13	23	0.10	0.15	0.20	0.10	0.10	0.10	24	40	24	NV	NV	10	11	00	00	10	40	36	NV	08	09
10	16	0.25	0.04	0.10	0.08	0.03	0.04	14	09	20	00	02	03	02	02	05	11	11	18	00	00	00
10	17	0.15	0.07	0.05	0.12	0.10	0.10	12	10	10	03	00	00	06	03	02	12	10	13	00	00	00

NV = No Value.

TABLE 1 (Continued)

NV = No Value.

TABLE 1 (Continued)

Subject		Glycine μg/mg Cr			Lysine μg/mg Cr			Taurine μg/mg Cr			Threonine μg/mg Cr			BCG acid .28 area (in²)			BCG acid .30 area (in²)		
		A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
22	33	22	10	14	16	07	05	14	10	20	11	00	00	.30	.17	.00	.00	.16	.00
22	34	27	18	24	05	05	10	04	00	00	10	00	13	.28	.21	.23	.00	.00	.00
14	25	18	08	08	33	14	18	23	32	21	23	14	15	.00	.00	.00	.00	.00	.00
14	24	13	08	08	44	23	30	16	14	20	19	19	13	.00	.00	.00	.00	.00	.00
23	35	14	20	12	12	14	10	14	20	23	11	15	00	.11	.12	.24	.00	.12	.11
23	36	12	09	20	10	07	10	10	27	14	10	00	13	.00	.29	.16	.00	.10	.00
24	37	67	110	63	48	89	18	30	80	400	23	NV	15	.00	.18	.16	.00	.00	.11
24	38	24	22	38	14	12	40	10	07	07	11	00	19	.18	.14	.19	.09	.12	.00
25	39	40	30	22	07	00	07	23	20	25	14	10	11	.20	.25	.13	.00	.00	.00
25	40	45	27	23	33	14	07	17	17	21	21	14	15	.12	.08	.20	.00	.00	.09
12	21	17	24	23	16	20	20	27	17	16	15	22	23	.17	.16	.13	.00	.00	.22
12	20	22	24	29	00	16	14	00	23	16	13	21	21	.20	.14	.18	.00	.00	.00
26	41	34	24	63	30	14	51	28	19	28	23	14	38	.13	.25	.22	.12	.08	.00
26	42	23	29	20	26	23	20	19	32	38	21	18	19	.10	.12	.23	.00	.00	.00
09	15	26	34	19	00	33	00	07	17	05	15	23	14	.16	.15	.24	.00	.00	.00
09	14	45	36	32	23	10	18	25	23	16	27	18	33	.11	.09	.14	.00	.00	.00
27	43	29	17	22	18	16	18	16	02	20	15	15	18	.32	.53	.52	.00	.22	.25
27	44	45	48	54	23	00	23	20	20	40	19	25	31	.00	.00	.00	.00	.00	.00
11	19	26	29	23	55	92	33	07	16	10	21	21	16	.20	.24	.24	.00	.00	.00
11	18	10	18	14	12	20	23	32	14	35	00	18	15	.21	.09	.14	.15	.00	.07
07	11	40	57	40	59	96	33	21	27	32	35	46	41	.12	.13	.42	.00	.00	.31
07	10	24	27	20	16	20	10	NV	25	25	25	19	14	.26	.25	.30	.00	.00	.00
28	45	48	38	71	55	59	63	60	32	40	23	18	22	.38	.12	.40	.15	.13	.00
28	46	89	38	57	55	14	20	23	19	19	33	19	25	.43	.18	.14	.00	.15	.00
29	47	30	36	27	10	16	12	32	25	10	19	19	22	.18	.19	.06	.00	.00	.00
29	48	51	34	54	18	12	12	02	14	05	25	15	14	.00	.00	.25	.00	.00	.00
08	13	08	16	13	00	44	12	05	53	17	13	27	15	.00	.26	.20	.00	.16	.00
08	12	06	15	17	10	23	16	00	19	49	11	19	21	.00	.17	.21	.00	.00	.00
13	22	12	24	17	14	00	18	05	00	00	19	23	22	.00	.00	.00	.00	.00	.00
13	23	28	20	13	NV	26	18	NV	17	10	NV	27	19	.09	.00	.00	.00	.00	.00
10	16	26	16	26	10	00	14	12	14	12	15	11	19	.14	.00	.00	.25	.00	.00
10	17	34	20	17	00	05	00	12	16	14	14	16	21	.16	.00	.18	.00	.28	.23

NV = No Value.

TABLE 1 (Continued)

Subject		BCG basic .32 area (in^2)			"Hippuric acid" area (in^2)			"Lactic acid" area (in^2)			DSA purple .90 area (in^2)			DSA orange .85 area (in^2)		
		A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
22	33	.52	.00	.53	.09	.22	.24	.00	.06	.27	.16	.13	.10	.18	.35	1.03
22	34	.22	.21	.26	.33	.32	.07	.11	.00	.00	NV	NV	.13	.58	.69	.28
14	25	.58	.37	.24	.22	.24	.37	.13	.19	.52	.34	.28	.42	.30	.00*	.16
14	24	.53	.20	.60	.61	.31	.12	.00	.22	.00	.27	.32	.34	.15	.40	.00
23	35	.00	.00	.00	.12	.22	.18	.00	.00	.07	.10	.35	.26	.27	.75	.65
23	36	.42	.00	.33	.29	.19	.18	.24	.00	.17	.17	.20	.29	.58	.63	.53
24	37	.50	.00	.00	.20	.29	.04	.48	.32	.07	.27	.26	.08	.29	.18	.00
24	38	.00	.00	.26	.00	.00	.02	.00	.00	.03	.12	.10	.29	.00	.14	.15
25	39	.00	.00	.36	.16	.21	.15	.00	.00	.00	.24	.27	.27	.40	.00	.00
25	40	.52	.41	.00	.08	.07	.29	.03	.09	.00	.25	.14	.23	.09	.25	.42
12	21	.29	.34	.00	.23	.44	.62	.16	.18	.17	.27	NV	NV	.28	.37	.41
12	20	.80	.20	.32	.30	.24	.34	.12	.00	.08	NV	.54	.24	.12	.17	.57
26	41	.00	.00	.33	.24	.32	.42	.54	.37	.65	.18	.19	.29	.16	.08	.48
26	42	.20	.16	.00	.34	.28	.41	.58	.53	.72	.30	.29	.30	.15	.00	.59
09	15	.60	.13	.49	.32	.10	.19	.29	.13	.23	.45	.35	.38	.48	.28	.32
09	14	.26	.25	.27	.21	.04	.29	.29	.00	.45	.24	.09	.25	.40	.37	.62
27	43	.00	.00	.00	.22	.20	.28	.35	.39	.53	.27	.30	.31	.53	.72	.46
27	44	.45	.81	.76	.18	.18	.15	.17	.57	.57	.22	.28	.32	.43	.44	.53
11	19	.31	.13	.28	.35	.29	.21	.00	.00	.23	.18	.16	.22	.21	.29	.20
11	18	.00	.40	.00	.00	.34	.22	.00	.00	.14	.21	.21	.24	.27	.36	.29
07	11	.20	.35	.00	.04	.27	.27	.52	.20	.36	.17	.20	.24	.00	.00	.00
07	10	.11	.19	.00	.19	.24	.16	.33	.39	.51	.18	.11	.08	.00	.00	.00
28	45	.00	.00	.00	.18	.29	.24	.21	.47	.58	.59	.77	.61	.50	.82	.57
28	46	.00	.00	.00	.20	.25	.25	.20	.11	.00	.30	.37	.32	.41	.15	.24
29	47	.00	.41	.52	.08	.09	.16	.27	.05	.08	.15	.17	.17	.20	.00	.00
29	48	.71	.73	.54	.07	.20	.10	.32	.34	.12	.09	.12	.10	.00	.00	.31
08	13	1.07	.00	.00	.13	.51	.34	.29	.40	.27	.22	.57	.27	.00	.26	.54
08	12	.83	.00	.00	.04	.31	.26	.19	.40	.46	.14	.47	.22	.00	.48	.27
13	22	.17	.57	.31	.39	.00	.25	.40	.10	.40	.23	.15	.27	.46	.18	.00
13	23	.49	.30	.13	.10	.39	.27	.00	.55	.64	NV	.39	.35	.00	.25	.21
10	16	.00	.43	.32	.20	.17	.57	.11	.00	.54	.23	.30	.34	.27	.00	1.14
10	17	.12	.00	.00	.46	.42	.35	.17	.05	.14	.29	.40	.29	.80	.64	.41

* In some instances where the value .00 appears, the substance was actually present but in quantities too small to form a discrete area.
NV = No Value.

(80 : 20 : 20) solvent.[2] The numerals indicate the Rf values at which these spots appear. "Hippuric acid" and "Lactic acid" refer to acid spots appearing on bromcresol green chromatograms at the expected position for the indicated acids. It is possible that other acids contribute to these spots, however. The substances designated "DSA orange .85" and "DSA purple .90" appear on chromatograms which have been sprayed with diazotized sulfanilic acid. The spots occuring on the bromcresol green and the diazotized sulfanilic acid (DSA) chromatograms have been quantified by carefully marking the area of the spots with a pencil and then measuring the area with a polar planimeter. In studies of the DSA spots, it has been found that over the range likely to be found in urine the area of the spot is approximately linearly related to the amount of material present. Occasionally the presence of salicylate metabolites prevented an accurate quantitative estimation of some of the substances detected chromatographically. In such cases, "no value (NV)" was recorded.

The optical density measurements were made by comparing the undiluted sediment-free samples with water in a spectrophotometer at 620 mμ.

RESULTS

The original measurements of the urinary constituents are presented in table 1. The mean and standard deviation for each item are shown in table 2. In most cases, the measurements have been expressed as creatinine ratios in table 2, since this ratio is a more significant quantity. For most of these items, no population norms have been established; however, no grossly abnormal samples were encountered and these measurements are comparable to those reported in other studies (Berry, '53; Beerstecher, et al., '50; Young, et al., '51). The lack of a comparable control group makes it impossible to detect any minor peculiarities which may be associated with this experimental group. Studies on this group will, however, give information on individual consistency and sibship similarities.

To test the reliability of the measurements as a function of individual differences, an analysis of variance was carried out considering the sample as composed of 32 individuals with three measures each. The F values

[2] The somewhat varying Rf values for these substances has resulted in different designations by different authors. Berry ('53) designates as "BCG acid .30" what is here called "BCG acid .28." She does not report on the spot here called "BCG acid .30."

TABLE 2

Analysis of variance for individual and intrasibship consistency of urinary excretion products

No.	Substance	Mean	σ	Individual Consistency			Intrasibship Consistency		
				F	d.f.	p	F	d.f.	p
1	DSA orange .85 (in^2)	.303	.251	2.282	64, 31	.005	9.691	16, 15	.001
2	Creatinine (mg/ml)	1.19	.63	5.317	64, 31	.001	4.045	16, 15	.01
3	BCG acid .28 (in^2)	.152	.121	3.545	64, 31	.01	1.409	16, 15	> .1
4	BCG acid .30 (in^2)	.038	.075	1.293	64, 31	> .1	1.102	16, 15	> .1
5	"Hippuric acid" (in^2)	.231	.131	1.645	64, 31	.05	4.109	16, 15	.01
6	Taurine (μg/mg Cr)*	23.3	41.1	1.771	60, 29	.05	0.768	14, 13	> .1
7	BCG basic .32 (in^2)	.233	.239	2.339	64, 31	.005	1.222	16, 15	> .1
8	Histidine·HCl (μg/ml)	118	56	5.426	64, 31	.001	2.430	16, 15	.05
9	Phosphorus (mg/mg Cr)	.797	.248	2.395	64, 31	.005	2.496	16, 15	.05
10	Optical density (x 1000/Cr)	15.7	20.7	3.828	64, 31	.001	4.906	16, 15	.005
11	Glutamic acid (μg/mg Cr)	2.48	3.34	2.129	56, 27	.01	1.797	13, 12	> .1
12	Lysine (μg/mg Cr)	21.1	19.9	4.024	62, 30	.001	1.602	15, 14	> .1
13	DSA purple .90 (in^2)	.264	.123	5.918	56, 27	.001	1.694	13, 12	> .1
14	"Lactic acid" (in^2)	.225	.203	3.774	64, 31	.001	4.948	16, 15	.005
15	Glycine (μg/mg Cr)	28.5	17.9	7.711	64, 31	.001	2.384	16, 15	.1
16	Specific gravity (−1, x10^3, /Cr)	18.9	7.1	2.577	64, 31	.005	3.680	16, 15	.01
17	Uric acid (mg/mg Cr)	.269	.163	3.407	64, 31	.001	3.083	16, 15	.05
18	pH	6.27	.64	2.077	64, 31	.01	1.781	16, 15	> .1
19	Ethanolamine (μg/mg Cr)	2.67	3.36	2.711	62, 30	.001	1.833	15, 14	> .1
20	β-Aminoisobutyric acid (μg/mg Cr)	5.48	5.25	5.124	42, 20	.001	10.445	11, 10	.001
21	Alanine (μg/mg Cr)	22.8	12.9	4.554	64, 31	.001	2.356	16, 15	.1
22	Glutamine (μg/mg Cr)	27.1	15.0	5.869	64, 31	.001	3.667	16, 15	.01
23	Threonine (μg/mg Cr)	17.8	8.47	4.365	60, 29	.001	2.663	14, 13	.05

* Cr = Creatinine.

are shown in table 2 with their levels of significance indicated. The high level of significance obtained for nearly every item certainly justifies the conclusion that even items falling within the middle of the normal range occur at levels characteristic of the particular individual.

A further hypothesis—whether or not siblings tend to resemble each other more than could be expected by chance—was tested by considering the sample to be made up of 16 groups of two individuals each. For this purpose the averages of the three measures were used as the value for that individual. These results are also shown in table 2. The larger number of substances failing to show significance may in part be due to the fact that higher F values are necessary to attain a given level of significance when the sample is reduced in size as it is in the intersibship comparison. Further work with a larger number of subjects will be necessary before conclusions can be drawn regarding the intrasibship similarity.

The origin of the intrasibship similarities would seem most probably to lie in their similar genetic makeup. The diet, which is the environmental variant most likely to influence the composition of the blood and urine, was fairly constant for all subjects because of their institutional status. Other studies (Thompson and Kirby, '49; Sutton, '51; Groen, et al., '52) have shown diet to be relatively unimportant in determining the levels of many body metabolites. The relative importance of heredity versus diet remains a subject for further study, however. Experiments are in progress in this laboratory which should throw additional light on this matter.

In order to have a quantitative measure of the degree of intrasibship concordance, the indices shown in table 3 have been calculated. The similarity index is the reciprocal of the mean square average difference in standard scores between siblings for all the items measured. The column headed "r_{12}" is the product moment correlation based on the 12 items of table 2 which showed an intrasibship similiarity significant at least at the 5% level. The column headed "r_{23}" is the correlation coefficient based on all 23 items of table 2. Inspection of the table reveals a fairly close agreement between the two correlations and the index of similarity. Part of the difference is undoubtedly due to the fact that the correlation coefficient places emphasis on congruence of the extreme values while the index of similarity places equal emphasis on congruence of intermediate and extreme values. A choice between these indices is difficult until more is known concerning the relative

importance to heredity of absolute levels versus related *patterns* of excretion. It is interesting to note that neither of the two sets of twins (sibships 08 and 13) ranks highest in similarity as calculated in table 3.

One interesting form in which individual variations occur is in the different *patterns* of urinary excretion. By this is meant the relative amount of each substance present when compared with other substances.

TABLE 3

Comparisons of profile similarities within sibships

Sibship	Sex	Index of Similarity	r_{12}	r_{23}
23	♂♂	11.6	.437	.350
22	♀♀	10.6	.563	.463
26	♂♂	9.8	.407	.339
10	♀♀	8.9	.432	.374
14	♂♂	8.4	.699	.538
13	♀♀	8.1	.625	.501
12	♀♀	7.8	.132	.042
29	♀♀	7.4	−.003	.206
25	♂♂	6.9	.301	.201
11	♂♀	6.8	.099	.058
09	♂♂	6.8	.396	.236
08	♀♀	6.3	.229	.169
28	♂♀	5.1	.175	.448
07	♀♀	3.7	.634	.323
27	♀♀	3.3	.180	−.308
24	♂♀	3.1	−.094	−.084

Figure 1 shows such individual patterns or profiles. The values plotted are the standard scores, obtained for each item by subtracting the group mean from the individual value and then dividing by the standard deviation. The results thus expressed are comparable from one substance to another. Sibships 22 and 23, whose profiles are shown in figure 1, possess a pattern observable to some extent in at least 10 of the 32 individuals studied. These similarities were first observed on graphs in which the items were plotted in a random sequence. In order to make the similarity more obvious, the individual items of the 4 subjects whose patterns were most nearly consistent with each other (sibships 22 and 23) were ranked in order of decreasing size for each subject. The average rank of each item was then obtained, and the sequence of items shown in figure 1 is in terms of these increasing average ranks.

STANDARD SCORE

FIG.

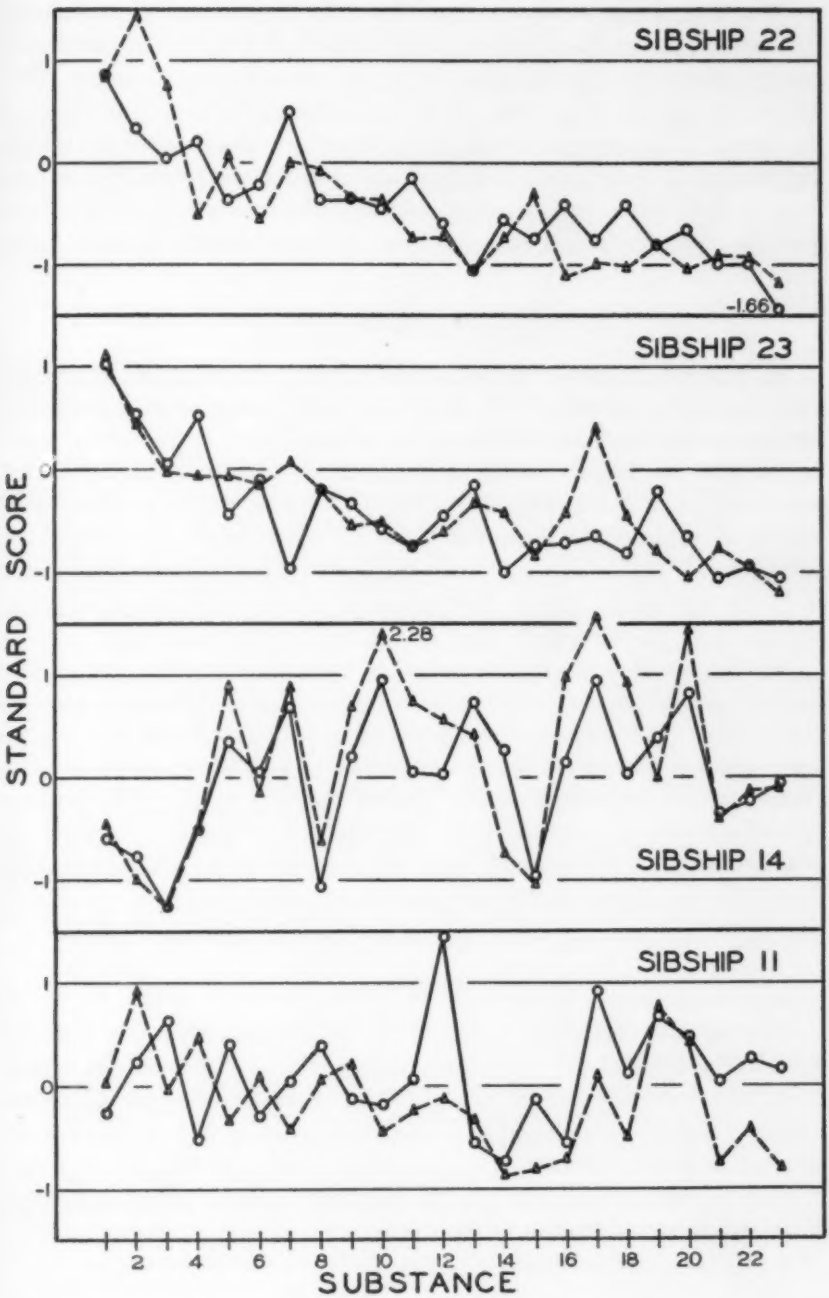

FIG. 1. PROFILES OF URINARY EXCRETION PATTERNS OF FOUR PAIRS OF SIBLINGS. THE SUBSTANCES ARE NUMBERED AS IN TABLE 2.

The resemblance between the profiles of sibships 22 and 23 is striking. By contrast, the profiles of sibship 14 seem to show a completely unrelated pattern, although the concordance within this sibship is high. The profiles of sibship 11 resemble those of sibships 22 and 23 for many of the items. The concordance of the siblings for the marked deviations which occur indicates that this deviation is not a matter of chance. At least three different patterns of excretion of the type discussed here have been found which were common to two or more sibships in this study.

DISCUSSION

Of particular interest in the past have been such anomalies of urinary excretion as alcaptonuria and cystinuria, conditions which are characterized by excretion of one or a few substances at levels many times higher than are usually found in a normal population. There probably are many such genetically controlled conditions whose presence goes unnoticed because the principal point of interference with metabolic processes lies too far removed from the easily measurable materials such as blood and urine. Many differences must also exist whose effect at any point in the metabolic processes is small.

By the use of such an approach as is presented here, it is hoped that some inroad can be made into the area of the integral differences between individuals. The detection of differences in *patterns* of excretion should provide a new means of classifying human beings, perhaps into discrete groups, which will make family studies more fruitful. The primary variables which are responsible for these profile differences are as yet not well understood. A statistical approach such as multiple factor analysis should furnish considerably more insight in this area.

SUMMARY

The urinary excretion products of 16 sib-pairs who are mentally deficient were analyzed chemically for creatinine, phosphorus, amino acids, and other substances which can be detected on paper chromatograms. Analysis of variance showed that most of the substances are excreted at levels characteristic of the individual and that siblings tend to resemble each other more than do unrelated persons. Several *patterns* of excretion were detected in the group.

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MATHEMATICAL ANALYSIS OF THE GROWTH OF MAN, WITH SPECIAL REFERENCE TO FORMOSANS [1]

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INTRODUCTION

THE growth of animals and plants consists of an increase of living substance resulting in cell division. A human ovum which has been fertilized and implanted in the uterus takes about 280 days to develop into a baby which, in turn, continues to grow after birth. It is well known that the rate of human growth is greatest during the first year of life, and that the body of the human species, like that of other animals, ceases to grow after a certain age. The weight of a human at birth doubles itself in about 5 months and trebles itself by the end of the first year.

The growth of the human body is three-dimensional, since it involves increase in the size of bones and other constituent organs. There has been a host of investigations on the growth of man which deal with the development of stature, chest girth, sitting height, span, weight and so forth. However, since the human body grows not only in one dimension, it is obvious that the growth of the body as a whole is most appropriately represented by the deevlopment of its weight, which is the resultant of the growth of the constituent organs. Therefore, body weight is the best index of growth.

With regard to the development of weight in man at different ages, there have been a great number of studies, of which the results are summarized by Baldwin ('21) and Davenport ('26A). Nevertheless, very

[1] Aided by a grant from The China Foundation, New York, N. Y.

few authors have attempted mathematically to analyze the development of body weight from birth to maturity. Although the process of human growth is of great complexity, it is conceivable that this process follows certain natural laws which can be expressed by mathematical formulas where the amount of growth y is the function of time x. Such formulas enable one to establish the norm of human growth, to foretell with considerable certainty the quantitative results of any future observations of a similar nature, and to form some idea of the causes of deviations between the calculated and observed results.

Robertson ('15), as the result of certain theoretical considerations, found that growth in the weight of infants followed the autocatalytic equation. Lambolez ('25) obtained an exponential equation to represent the law of growth in infants. Failing to analyze the developmental curve of body weight as it is, Davenport ('26B) transformed it into a curve of annual increments of total body weight and concluded that this latter curve has two autocatalytic cycles, one being best fitted by a theoretical skew curve of Pearson's type I and the other by a normal frequency curve.

The curve of the development of weight from birth to maturity shows the same shape, roughly similar to a sigmoid, not only for Americans (Baldwin, '21 and Watson and Lowrey, '52) and Nordics (Davenport, '26A and '26B) but also for Chinese (Shirokogoroff, '25) and Japanese (Yoshinaga, '30 and Department of Physical Education, '27), except that the slope of the curve varies with race and sex. In view of the fact that no one so far has carried out any study on the physical growth of the Formosans from birth to maturity, it is of great interest first to collect as many data as possible for calculating the average weight of Formosans of both sexes at different ages, and then to analyze the weight curve to find the mathematical formulas that will serve as the norm of growth of the Formosans. Although the slope of the Formosan growth curve is different from that of others, the mathematical formulas obtained can be applied to other races when the various constants of the formulas are separately computed.

PROBLEMS FOR SOLUTION

In the mathematical analysis of the growth of Formosans, it is proposed that a number of problems which are important and interesting to various specialties of medical science and public health (physiology, anthropology, obstetrics, maternal and child health, pediatrics, school

health, internal medicine, and physical education) be solved at the same time. These problems and the specialties closely related to them are summarized in table 1. Although some of these problems may be readily solved if only the mathematical formulas for the entire growth curve are obtained, still further analysis of the curve is needed in order to find the solution to the other problems.

TABLE 1

Problems to be Solved

NO.	PROBLEM
I	What course does the growth of man take in his lifetime?
II	What is the average birth weight of the Formosans?
III	What is the normal growth of Formosan infants?
IV	What is the normal growth of Formosan children of preschool age?
V	What is the normal growth of Formosan school children?
VI	What is the normal growth of Formosans from adolescence up to adulthood?
VII	What is the maximum limit of growth of the Formosans?
VIII	At what age does the adolescence of the Formosans start?
IX	At what age does the rate of adolescent growth of the Formosans reach its maximum?
X	At what age do the Formosans stop growing?

MATERIAL

Inasmuch as the physical growth of the Formosans has never been studied from birth to maturity, the weight data for the two sexes and different ages had to be collected from various sources which could be regarded as reliable. For the birth weight, the data obtained in 1942 by Wu ('49) and those in 1950 by Chiu and his coworkers ('51) have been utilized to calculate the mean. For the weight at each month of infancy, the data acquired by Wu ('49) have been used. For later years the data of the health survey collected in 1938 by the Department of Health of the Government-General of Formosa were used.[2] In all, data

[2] It has been assumed that mean body weights of different persons at these various ages adequately represent the weight differences of a single group of persons successively observed at these ages. While some discrepancy might appear between these two types of observation, it would affect only the evaluation of the constants in the following formulas, and not the mode of analysis itself.

concerning 87,277 Formosan males and 83,376 Formosan females have been used in the present study. Table 2 presents the mean weight and the number of persons observed for each month of the first year and for each subsequent year of life.

Figure 1 shows the growth curve of Formosan males and females plotted by using the average weights at different ages from table 2. Growth curves of Americans (Watson and Lowrey, '52), Nordics (Davenport, '26A and B) and Japanese (Yoshinaga, '30 and Department of Physical Education, '27) are presented in figures 2 to 4 by the use of the data derived from the respective sources cited. The dots in all these curves represent the average weights actually observed.

METHOD OF ANALYSIS

On looking at the growth curves in figures 1 through 4, it is obvious that there are more than two cycles in the course of human growth from birth to maturity, although its curve looks roughly like a sigmoid. During the first year of life, there exists a cycle of rapid growth. The curve then begins to flatten out until about 5 years of age when it rises more rapidly again. It reaches a maximum of slope in this cycle at 12 to 14 years and then gradually approaches the horizontal which indicates the state of maturity.

The mathematical analysis of human growth consists in finding out from the observed results the mathematical formulas that express certain natural laws. If the human growth curve were a straight line, then the required formula would be $y = a + bx$, which is the general equation of a straight line; the values of the constants a and b can be found by simple calculation. However, as the growth of man demonstrates a complicated curve having more than two cycles, it is quite clear that a single formula is not enough to express it. There should be as many formulas as there are cycles involved in the whole curve. It is extremely difficult to find the formula for each cycle from the shape of the curve, since it is, as a rule, impossible to tell by mere inspection whether the portion of the curve belongs to a parabola, a hyperbola, a logarithmic curve, an exponential or a trigonometric curve. The required formula must in such cases be obtained by trial. Generally one has some sort of idea as to what kind of formula to expect, and in order to test the correctness of one's expectations one can attempt to convert the curve into a straight line by means of certain artifices, such as transformation of the coordinates, use of a trial value for some constant of

TABLE 2

Observed Average Weight of Formosans

AGE IN YEARS	MALE		FEMALE	
	Number of Persons Observed	Average Weight in Kilograms	Number of Persons Observed	Average Weight in Kilograms
Birth	280	3.131	215	3.065
1/12	100	4.200	71	4.041
2/12	274	5.250	264	4.995
3/12	317	5.896	286	5.549
4/12	423	6.462	455	6.014
5/12	519	6.942	437	6.460
6/12	519	7.263	476	6.853
7/12	576	7.554	467	7.139
8/12	433	7.835	288	7.427
9/12	337	8.100	232	7.704
10/12	228	8.318	140	7.973
11/12	190	8.517	136	8.166
1	234	8.718	149	8.438
2	3 648	11.003	3 591	10.909
3	3 530	12.769	3 376	12.203
4	3 459	14.194	3 295	13.744
5	3 210	15.619	3 124	15.000
6	3 033	16.931	2 898	16.316
7	2 995	18.323	2 925	17.869
8	2 914	19.808	2 925	19.481
9	2 987	21.739	2 850	21.334
10	2 889	23.561	2 786	23.314
11	2 798	25.084	2 656	25.489
12	2 753	27.608	2 580	28.125
13	2 545	30.008	2 523	31.474
14	2 497	33.409	2 525	35.321
15	2 157	37.478	2 239	39.690
16	2 250	41.389	2 167	42.154
17	2 299	44.138	2 321	44.036
18	2 292	46.905	2 196	45.765
19	2 124	49.208	2 113	46.286
20	2 168	50.884	2 189	46.586
21	1 973	51.638	1 905	47.220
22	1 914	52.444	1 832	46.849
23	1 819	52.699	1 843	47.138
24	1 944	52.830	1 847	47.183
25–29	8 338	53.111	7 971	47.719
30–34	7 607	53.318	6 936	47.434
35–39	6 704	53.246	6 147	47.284
Total	87 277		83 376	

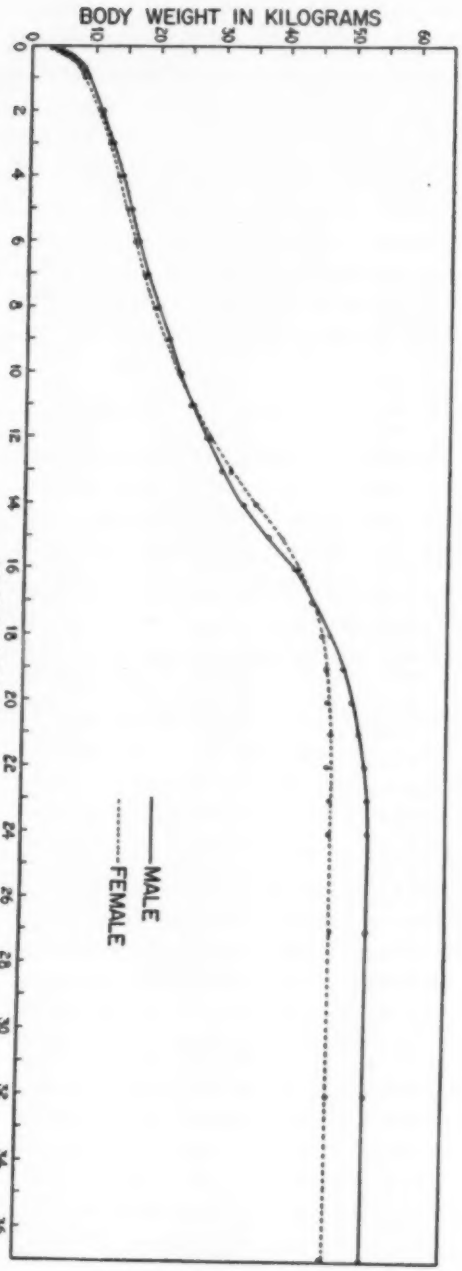

FIG. 1. GROWTH OF FORMOSANS

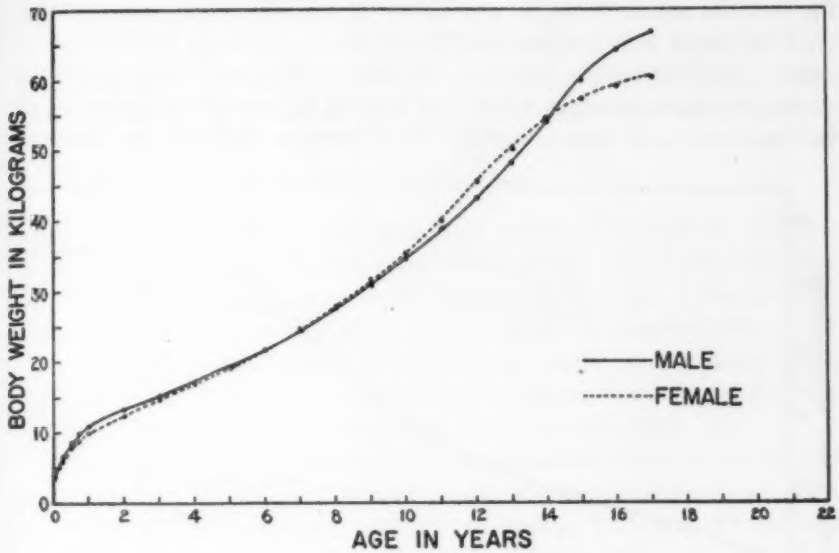

FIG. 2. GROWTH OF AMERICANS

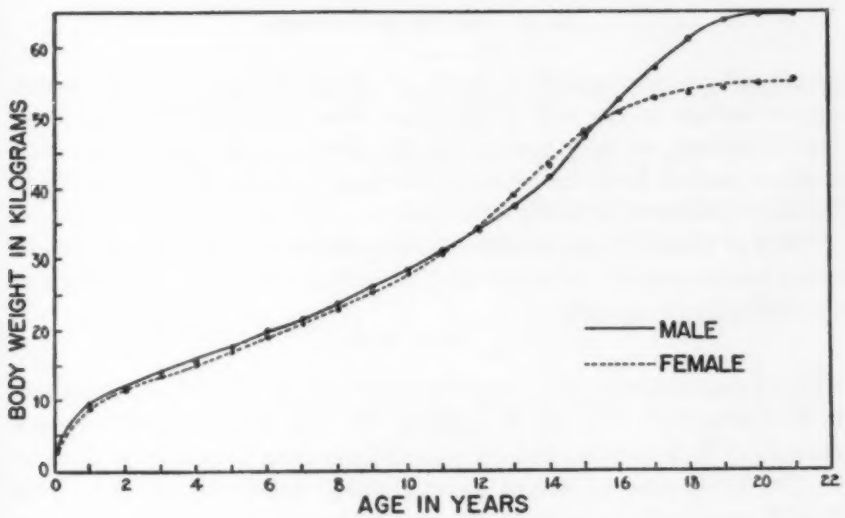

FIG. 3. GROWTH OF NORDICS

the formula, etc. If the attempt is successful, then all the constants of the formula assumed can be calculated by the method of least squares.

This is but a first approximation of the constants to the theoretical curve. It is desirable, however, to obtain the best-fitting curve by successive approximations which will correct the computed values of all the constants and thus minimize the differences between the observed

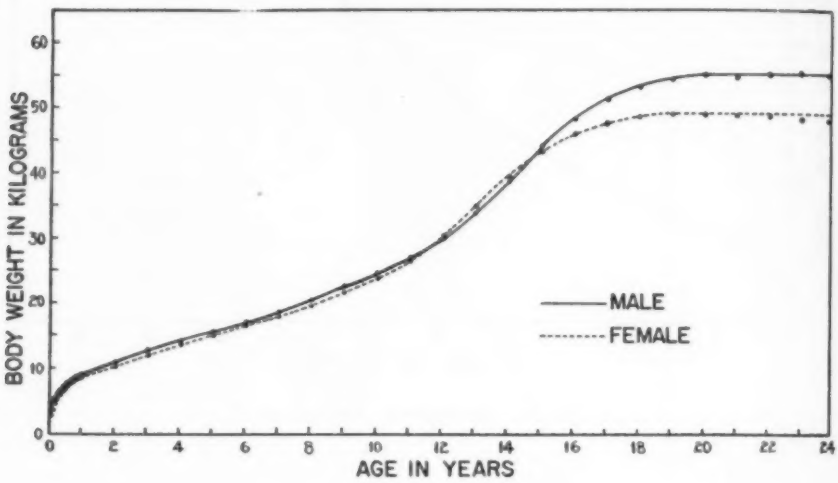

FIG. 4. GROWTH OF JAPANESE

points and the corresponding points on the fitted curve. If the second approximation to the best-fitting curve does not sufficiently minimize the deviations, we may proceed to the third and the fourth approximations, and so forth, by repeating the same process, till the best fit to the observed curve is finally attained.

It was found, by the procedure stated above, that the human growth curve has four cycles, of which the first and second cycles are best fitted by the catalytic equation

$$y = k - e^{a-bx}$$

where y represents weight, x denotes time and k, a and b are constants to be determined. For the Formosans, the first cycle of growth ranges from birth to 9 months, and the second cycle from 9 months to 5 years.

The third cycle of human growth, which was found to range from 5 to 13 years in Formosans, is best represented by the compound interest equation

$$y = e^{a+bx}$$

in which y and x denote weight and time respectively, and a and b are constants to be calculated.

The fourth growth cycle of the Formosans extends from 13 years till maturity, at which the body ceases to grow. The best-fitting curve to the fourth cycle of human growth is the logistic equation

$$y = d + \frac{k}{1 + e^{a+bx}}$$

where y represents weight, x denotes time, and d, k, a and b are constants to be determined. Among these four constants, d is the lower asymptote which denotes the total growth attained up to the end of the previous growth cycle, $d + k$ is the upper asymptote of the present cycle, b the inherent rate constant, and a the constant of integration dependent upon the position of the origin. The method of determining these constants is fully described in a previous paper of the writer (Quo, '50).

The constants of the above theoretical equations obtained by the first approximation should be subjected to further approximations in order to get the best fit to the observed growth curve. The observed curve of a given growth cycle may be expressed by the equation

$$y' = f(u, v, w; x)$$

where u, v and w are the unknown constants to be determined. Then the equation obtained from the first approximation is

$$Y_1 = f(u_1, v_1, w_1; x)$$

in which u_1, v_1 and w_1 are the first estimated values of the constants. Therefore

$$u = u_1 + c_1; \quad v = v_1 + c_2; \quad w = w_1 + c_3$$

where c_1, c_2 and c_3 are the correction terms that will be calculated from a subsequent approximation. By the expansion of Taylor's theorem, we get

$$\begin{aligned} f(u, v, w; x) = f(u_1, v_1, w_1; x) &+ (u - u_1)\frac{\partial f}{\partial u_1} + (v - v_1)\frac{\partial f}{\partial v_1} \\ &+ (w - w_1)\frac{\partial f}{\partial w_1} + \frac{1}{2}\Big[(u - u_1)^2\frac{\partial^2 f}{\partial u_1^2} + (v - v_1)^2\frac{\partial^2 f}{\partial v_1^2} \\ &+ (w - w_1)^2\frac{\partial^2 f}{\partial w_1^2}\Big] + \Big[(v - v_1)(w - w_1)\frac{\partial^2 f}{\partial v_1 \partial w_1} \\ &+ (u - u_1)(w - w_1)\frac{\partial^2 f}{\partial u_1 \partial w_1} + (u - u_1)(v - v_1)\frac{\partial^2 f}{\partial u_1 \partial v_1}\Big] \\ &+ \cdots. \end{aligned}$$

Neglecting terms of higher order than the first, we have

$$y - y' - Y_1 = c_1 \frac{\partial f}{\partial u_1} + c_2 \frac{\partial f}{\partial v_1} + c_3 \frac{\partial f}{\partial w_1}$$

which is a linear expression for the correction terms. Therefore, we fit regression

$$y - y' - Y_1 = c_1 x_1 + c_2 x_2 + c_3 x_3$$

in which

$$x_1 = \frac{\partial f}{\partial u_1}, \quad x_2 = \frac{\partial f}{\partial v_1}, \quad x_3 = \frac{\partial f}{\partial w_1}.$$

The values of c_1, c_2 and c_3 are to be determined by the method of least squares.

Now for the catalytic equation, we have

$$f = k - e^{a - bx},$$

therefore

$$\frac{\partial f}{\partial k_1} = 1,$$

$$x_1 = \frac{\partial f}{\partial a_1} = -e^{a_1 - b_1 x} = -(k_1 - Y_1),$$

$$x_2 = \frac{\partial f}{\partial b_1} = x e^{a_1 - b_1 x} = x(k_1 - Y_1),$$

where a_1, b_1, k_1 and Y_1 are respectively the estimated values of a, b, k and y from the first approximation.

Let $c_0 = k_2 - k_1$; $c_1 = a_2 - a_1$; $c_2 = b_2 - b_1$, in which k_2, a_2 and b_2 are the values of the constants that will be calculated from the second approximation. Then we fit regression

$$y - y' - Y_1 = c_0 + c_1 x_1 + c_2 x_2$$

where y' denotes the observed weight. By the method of least squares, we choose c_0, c_1 and c_2 to minimize

$$f = \Sigma (y - c_0 - c_1 x_1 - c_2 x_2)^2.$$

Hence

$$\frac{\partial f}{\partial c_0} = -2\Sigma (y - c_0 - c_1 x_1 - c_2 x_2) = 0,$$

whence

$$c_0 = \bar{y} - c_1 \bar{x}_1 - c_2 \bar{x}_2,$$

in which $\bar{y}$, $\bar{x}_1$ and $\bar{x}_2$ are respectively the means of y, x_1 and x_2.

Similarly $$\frac{\partial f}{\partial c_1} = -2\Sigma x_1(y - c_0 - c_1x_1 - c_2x_2) = 0,$$

and $$\frac{\partial f}{\partial c_2} = -2\Sigma x_2(y - c_0 - c_1x_1 - c_2x_2) = 0.$$

On substitution for c_0, we get

$$\begin{aligned}\Sigma x_1(y - c_0 - c_1x_1 - c_2x_2) &= \Sigma x_1(y - \bar{y} + c_1\bar{x}_1 + c_2\bar{x}_2 - c_1x_1 - c_2x_2)\\ &= \Sigma x_1(y - \bar{y}) - c_1\Sigma x_1(x_1 - \bar{x}_1) - c_2\Sigma x_1(x_2 - \bar{x}_2)\\ &= 0.\end{aligned}$$

Hence $$c_1\Sigma x_1(x_1 - \bar{x}_1) + c_2\Sigma x_1(x_2 - \bar{x}_2) = \Sigma x_1(y - \bar{y})$$

which is identical with

$$c_1\Sigma(x_1 - \bar{x}_1)^2 + c_2\Sigma(x_1 - \bar{x}_1)(x_2 - \bar{x}_2) = \Sigma(x_1 - \bar{x}_1)(y - \bar{y}) \quad \text{(A)}.$$

Similarly

$$\begin{aligned}\Sigma x_2(y - c_0 - c_1x_1 - c_2x_2) &= \Sigma x_2(y - \bar{y}) - c_1\Sigma x_2(x_1 - \bar{x}_1) - c_2\Sigma x_2(x_2 - \bar{x}_2)\\ &= 0.\end{aligned}$$

Therefore $$c_1\Sigma x_2(x_1 - \bar{x}_1) + c_2\Sigma x_2(x_2 - \bar{x}_2) = \Sigma x_2(y - \bar{y})$$

which is same as

$$c_1\Sigma(x_1 - \bar{x}_1)(x_2 - \bar{x}_2) + c_2\Sigma(x_2 - \bar{x}_2)^2 = \Sigma(x_2 - \bar{x}_2)(y - \bar{y}) \quad \text{(B)}.$$

Equations (A) and (B) may be written

$$c_1s_{11} + c_2s_{12} = s_{1y} \qquad c_1s_{12} + c_2s_{22} = s_{2y}$$

which are the normal equations whose solution gives the values of the correction terms c_1 and c_2. The value of c_0 can be easily derived from these terms.

We may repeat this procedure, as well as those described below, for further approximations, till the best fit to the observed curve is obtained.

For the second approximation to the compound interest equation, we put

$$f = e^{a+bx}.$$

Therefore $$x_1 = \frac{\partial f}{\partial a_1} = e^{a_1+b_1x} = Y_1,$$

$$x_2 = \frac{\partial f}{\partial b_1} = xe^{a_1+b_1x} = xY_1$$

in which a_1, b_1, and Y_1 are respectively the calculated values of a, b and y from the first approximation. We fit regression

$$y = y' - Y_1 = c_1x_1 + c_2x_2,$$

where $c_1 = a_2 - a_1$, $c_2 = b_2 - b_1$, and y' is the observed weight. By the method of least squares, we choose c_1 and c_2 to minimize

$$f = \Sigma(y - c_1x_1 - c_2x_2)^2.$$

Hence $$\frac{\partial f}{\partial c_1} = -2\Sigma x_1(y - c_1x_1 - c_2x_2) = 0$$

and $$\frac{\partial f}{\partial c_2} = -2\Sigma x_2(y - c_1x_1 - c_2x_2) = 0,$$

whence $$c_1\Sigma x^2{}_1 + c_2\Sigma x_1x_2 = \Sigma x_1y$$

$$c_1\Sigma x_1x_2 + c_2\Sigma x^2{}_2 = \Sigma x_2y,$$

which may be written

$$c_1s_{11} + c_2s_{12} = s_{1y} \qquad c_1s_{12} + c_2s_{22} = s_{2y}.$$

These are the normal equations whereby the values of the correction terms c_1 and c_2 can be easily computed.

For the second approximation to the logistic equation, we have

$$f = d + \frac{k}{1 + e^{a+bx}},$$

hence

$$x_1 = \frac{\partial f}{\partial k_1} = \frac{1}{1 + e^{a_1+b_1x}} = \frac{Y_1 - d_1}{k_1},$$

$$x_2 = \frac{\partial f}{\partial a_1} = \frac{-k_1e^{a_1+b_1x}}{(1 + e^{a_1+b_1x})^2} = -\frac{(Y_1 - d_1)[k_1 - (Y_1 - d_1)]}{k_1},$$

$$x_3 = \frac{\partial f}{\partial b_1} = \frac{-xk_1e^{a_1+b_1x}}{(1 + e^{a_1+b_1x})^2} = -\frac{x(Y_1 - d_1)[k_1 - (Y_1 - d_1)]}{k_1},$$

$$x_4 = \frac{\partial f}{\partial d_1} = 1,$$

where Y_1, d_1, k_1, a_1 and b_1 represent respectively the estimated values of y, d, k, a and b from the first approximation.

Let $c_1 = k_2 - k_1$; $c_2 = a_2 - a_1$; $c_3 = b_2 - b_1$; $c_4 = d_2 - d_1$ in which k_2, a_2, b_2 and d_2 are the values of the constants to be calculated from the second approximation. Then we fit regression

$$y = y' - Y_1 = c_1x_1 + c_2x_2 + c_3x_3 + c_4x_4,$$

where y' denotes the observed weight. The values of the four correction terms c_1, c_2, c_3 and c_4 can be calculated from the following normal equations which are obtained by the same method of least squares as already described:

$$c_1 s_{11} + c_2 s_{12} + c_3 s_{13} + c_4 s_{14} = s_{1y}$$
$$c_1 s_{12} + c_2 s_{22} + c_3 s_{23} + c_4 s_{24} = s_{2y}$$
$$c_1 s_{13} + c_2 s_{23} + c_3 s_{33} + c_4 s_{34} = s_{3y}$$
$$c_1 s_{14} + c_2 s_{24} + c_3 s_{34} + c_4 s_{44} = s_{4y}.$$

These simultaneous equations are most readily solved by the determinants given below.

$$c_1 = \frac{\begin{vmatrix} s_{1y} & s_{12} & s_{13} & s_{14} \\ s_{2y} & s_{22} & s_{23} & s_{24} \\ s_{3y} & s_{23} & s_{33} & s_{34} \\ s_{4y} & s_{24} & s_{34} & s_{44} \end{vmatrix}}{\begin{vmatrix} s_{11} & s_{12} & s_{13} & s_{14} \\ s_{12} & s_{22} & s_{23} & s_{24} \\ s_{13} & s_{23} & s_{33} & s_{34} \\ s_{14} & s_{24} & s_{34} & s_{44} \end{vmatrix}}, \quad c_2 = \frac{\begin{vmatrix} s_{11} & s_{1y} & s_{13} & s_{14} \\ s_{12} & s_{2y} & s_{23} & s_{24} \\ s_{13} & s_{3y} & s_{33} & s_{34} \\ s_{14} & s_{4y} & s_{34} & s_{44} \end{vmatrix}}{\begin{vmatrix} s_{11} & s_{12} & s_{13} & s_{14} \\ s_{12} & s_{22} & s_{23} & s_{24} \\ s_{13} & s_{23} & s_{33} & s_{34} \\ s_{14} & s_{24} & s_{34} & s_{44} \end{vmatrix}}, \quad c_3 = \frac{\begin{vmatrix} s_{11} & s_{12} & s_{1y} & s_{14} \\ s_{12} & s_{22} & s_{2y} & s_{24} \\ s_{13} & s_{23} & s_{3y} & s_{34} \\ s_{14} & s_{24} & s_{4y} & s_{44} \end{vmatrix}}{\begin{vmatrix} s_{11} & s_{12} & s_{13} & s_{14} \\ s_{12} & s_{22} & s_{23} & s_{24} \\ s_{13} & s_{23} & s_{33} & s_{34} \\ s_{14} & s_{24} & s_{34} & s_{44} \end{vmatrix}},$$

$$c_4 = \frac{\begin{vmatrix} s_{11} & s_{12} & s_{13} & s_{1y} \\ s_{12} & s_{22} & s_{23} & s_{2y} \\ s_{13} & s_{23} & s_{33} & s_{3y} \\ s_{14} & s_{24} & s_{34} & s_{4y} \end{vmatrix}}{\begin{vmatrix} s_{11} & s_{12} & s_{13} & s_{14} \\ s_{12} & s_{22} & s_{23} & s_{24} \\ s_{13} & s_{23} & s_{33} & s_{34} \\ s_{14} & s_{24} & s_{34} & s_{44} \end{vmatrix}}.$$

RESULTS

The mathematical analysis by the writer of different human weight curves revealed that human growth, regardless of race and sex, is composed of 4 cycles, namely two catalytic cycles, a compound interest and a logistic, passing from one cycle to the other without abrupt transition. The general equation for each cycle is the same for all races and both sexes, but the constants of the equation vary due to the fact that the slope of the portion of the curve differs with sex and race. Slight

variations in the duration of growth cycles are observed among different races.

The durations and the final equations for the 4 cycles of the theoretical growth curve of Formosans are shown below. These equations enable one to predict the normal average weight for the two sexes at any age from birth to maturity.

First Cycle: Catalytic Growth

General Equation:

$$y = k - e^{a-bx}$$

or $$y = k - Ae^{-bx}$$

Formosans:

Period: from birth to 9 months

Equation:

Male $$y = 8.8 - e^{1.7243-0.2172x} \quad (1)$$

or $$y = 8.8 - 5.6088e^{-0.2172x} \quad (2)$$

Female $$y = 8.5 - e^{1.6870-0.1988x} \quad (3)$$

or $$y = 8.5 - 5.4034e^{-0.1988x} \quad (4)$$

Second Cycle: Catalytic Growth

General Equation:

$$y = k - e^{a-bx}$$

or $$y = k - Ae^{-bx}$$

Formosans:

Period: from 9 months to 5 years

Equation:

Male $$y = 21.5 - e^{2.7390-0.1913x} \quad (5)$$

or $$y = 21.5 - 15.4722e^{-0.1913x} \quad (6)$$

Female $$y = 20.5 - e^{2.6873-0.1958x} \quad (7)$$

or $$y = 20.5 - 14.6928e^{-0.1958x} \quad (8)$$

Third Cycle: Compound Interest Growth

General Equation:

$$y = e^{a+bx}$$

or $$y = Ae^{bx}$$

Formosans:

Period: from 5 years to 13 years

Equation:

Male $y = e^{2.34034+0.08135x}$ (9)

or $y = 10.3851e^{0.08135x}$ (10)

Female $y = e^{2.24202+0.09146x}$ (11)

or $y = 9.4126e^{0.09146x}$ (12)

Fourth Cycle: Logistic Growth

General Equation:

$$y = d + \frac{k}{1 + e^{a+bx}}$$

or $$y = d + \frac{k}{1 + Ae^{bx}}$$

Formosans:

Period: from 13 years onwards

Equation:

Male $$y = 19 + \frac{34.5}{1 + e^{1.21071-0.44726x}} \quad (13)$$

or $$y = 19 + \frac{34.5}{1 + 3.3559e^{-0.44726x}} \quad (14)$$

Female $$y = 22 + \frac{25.5}{1 + e^{1.06866-0.59474x}} \quad (15)$$

or $$y = 22 + \frac{25.5}{1 + 2.9115e^{-0.59474x}} \quad (16)$$

Note: y = body weight in kilograms

x = age in months for equations (1) to (4)

x = age in years for equations (5) to (12)

x = age in years -12 for equations (13) to (16).

The normal average weight of the Formosans at any time of life can be obtained by solving the above equations. Table 3 presents the normal average weight, both actually observed and theoretically calculated, of Formosans at each age. In the light of the small deviations of the computed values from the observed, it is clear that equations (1) through (16) excellently fit the 4 growth cycles of Formosans.

TABLE 3

Average Weight of Formosans as Observed and as Theoretically Calculated

AGE IN YEARS	MALE WEIGHT IN KILOGRAMS			FEMALE WEIGHT IN KILOGRAMS		
	Observed	Calculated	Deviations (Obs.-Calc.)	Observed	Calculated	Deviations (Obs.-Calc.)
Birth	3.131	3.191	−0.060	3.065	3.097	−0.032
1/12	4.200	4.286	−0.086	4.041	4.071	−0.030
2/12	5.250	5.167	0.083	4.995	4.870	0.125
3/12	5.896	5.877	0.019	5.549	5.524	0.025
4/12	6.462	6.447	0.015	6.014	6.061	−0.047
5/12	6.942	6.907	0.035	6.460	6.501	−0.041
6/12	7.263	7.276	−0.013	6.853	6.861	−0.008
7/12	7.554	7.574	−0.020	7.139	7.157	−0.018
8/12	7.835	7.813	0.022	7.427	7.399	0.028
9/12	8.100	8.096	0.004	7.704	7.597	0.107
10/12	8.318	8.308	0.010	7.973	8.019	−0.046
11/12	8.517	8.518	−0.001	8.166	8.223	−0.057
1	8.718	8.722	−0.004	8.438	8.421	0.017
2	11.003	10.947	0.056	10.909	10.569	0.340
3	12.769	12.784	−0.015	12.203	12.335	−0.132
4	14.194	14.302	−0.108	13.744	13.788	−0.044
5	15.619	15.597	0.022	15.000	14.981	0.019
6	16.931	16.919	0.012	16.316	16.293	0.023
7	18.323	18.353	−0.030	17.869	17.854	0.015
8	19.808	19.908	−0.100	19.481	19.564	−0.083
9	21.739	21.595	0.144	21.334	21.437	−0.103
10	23.561	23.426	0.135	23.314	23.490	−0.176
11	25.084	25.411	−0.327	25.489	25.740	−0.251
12	27.608	27.565	0.043	28.125	28.205	−0.080
13	30.008	29.967	0.041	31.474	31.784	−0.310
14	33.409	33.545	−0.136	35.321	35.519	−0.198
15	37.478	37.379	0.099	39.690	39.127	0.563
16	41.389	41.103	0.286	42.154	42.083	0.071
17	44.138	44.394	−0.256	44.036	44.197	−0.161
18	46.905	47.065	−0.160	45.765	45.565	0.200
19	49.208	49.089	0.119	46.286	46.395	−0.109
20	50.884	50.543	0.341	46.586	46.878	−0.292
21	51.638	51.549	0.089	47.220	47.153	0.067
22	52.444	52.227	0.217	46.849	47.307	−0.458
23	52.699	52.675	0.024	47.138	47.393	−0.255
24	52.830	52.968	−0.138	47.183	47.441	−0.258
25–29	53.111	53.359	−0.248	47.719	47.490	0.229
30–34	53.318	53.485	−0.167	47.434	47.499	−0.065
35–39	53.246	53.498	−0.252	47.284	47.500	−0.216

DISCUSSION

Growth consists of an increase in the number of tissue cells as a result of cell division. Hence it follows that growth takes place according to geometric progression in some form or other. Food material, ingested and assimilated in the body, is absorbed into the blood and carried to the various tissues of the body where it is partly used up, and partly transformed into the components of the tissue cells, such as nuclear material and cytoplasm, which are utilized in cell division to build up new cells. This biochemical transformation of food material is caused by the catalytic action of enzymes, which have vitamines as active components and are regulated by hormones.

In chemical reaction by catalysis, the reaction velocity $\frac{dy}{dx}$ at any instant is proportional to the amount of material present at that moment, i. e.,

$$\frac{dy}{dx} = b(k - y)$$

where y represents the amount of material transformed at time x, k denotes the original amount of material, b is the proportionality constant and $k - y$ equals the amount of material which remains untransformed at time x. This differential equation may be written

$$\frac{dy}{k - y} = b\,dx.$$

Integrating,

$$\int \frac{dy}{k - y} = b \int dx,$$

we get $$-\log_e(k - y) + c = bx + c',$$

or $$\log_e(k - y) = -bx + c - c',$$

where c and c' are constants of integration.

Put $$a = c - c',$$

then $$\log_e(k - y) = a - bx.$$

Hence $$y = k - e^{a - bx},$$

or $$y = k - Ae^{-bx} \qquad (A = e^a),$$

both equations expressing the two catalytic cycles of human growth.

Since growth is due to geometric increase in the number of tissue cells, it can also be considered from another aspect of the chemical reaction which occurs in the tissue to synthesize nuclear material and cytoplasm. The reaction velocity $\frac{dy}{dx}$ at any instant x is also proportional to the amount of the product, y, formed by the reaction at that moment. If this proportionality is converted into an equality by insertion of a proportionality constant b, we obtain the differential equation for the rate of formation of the product by the reaction, namely,

$$\frac{dy}{dx} = by.$$

Separating the variables,

$$\frac{dy}{y} = b dx,$$

and integrating,

$$\int \frac{dy}{y} = b \int dx,$$

we get $$\log_e y + c = bx + c'.$$

Putting $$a = c' - c,$$

we have $$\log_e y = a + bx.$$

Therefore $$y = e^{a+bx},$$

or $$y = Ae^{bx} \qquad (A = e^a),$$

which are the equations expressing the compound interest law in Nature. The third cycle of human growth follows this law.

The logistic equation, discovered by Verhulst (1838, 1845, 1847) and independently by Pearl and Reed ('20, '22, '23), gives an S-shaped curve with an upper and a lower asymptote and describes accurately the growth trend of human populations which cannot surpass its upper limit in a growth cycle. The fourth cycle of human growth is best expressed by the logistic equation. It is of considerable interest that the growth of human individuals from adolescence to maturity follows the same logistic law as the growth of human populations.

The maximum limit to the growth in man is represented by the upper asymptote of the logistic curve, $d + k$, of which d is the lower asymptote of the fourth cycle and k corresponds to the total amount of growth attained in the same cycle. Therefore, the maximum limit to the growth of the Formosans for each sex is

Male $d + k = 19 + 34.5 = 53.5$ Kilograms,

Female $d + k = 22 + 25.5 = 47.5$ Kilograms.

Since the logistic growth cycle extends from adolescence to adulthood, we can calculate the age of maximum rate of adolescent growth by finding the coordinates of the point where the rate of growth is a maximum. This point is the point of inflection of the logistic curve. After that point is passed, the rate of growth declines progressively, till finally the curve stretches along horizontally in close approach to the upper asymptote, over which the body cannot grow. Now the logistic equation to the fourth cycle of human growth is

$$y = d + \frac{k}{1 + e^{a+bx}}.$$

We put $$z = y - d = \frac{k}{1 + e^{a+bx}},$$

then
$$z' = \frac{dz}{dx} = \frac{-kbe^{a+bx}}{(1 + e^{a+bx})^2}$$
$$= \frac{kb - kb - kbe^{a+bx}}{(1 + e^{a+bx})^2}$$
$$= \frac{bz^2 - kbz}{k},$$

which is the equation to the first derivative curve. Therefore

$$z'' = \frac{1}{k}(2bz - kb)z' = 0.$$

At the point of inflection evidently z' is not equal to zero, hence

$$z = \frac{k}{2},$$

and $$y = \frac{k}{2} + d.$$

Therefore $$1 + e^{a+bx} = 2,$$

and $$x = -\frac{a}{b}.$$

Accordingly, the age at which the maximum rate of adolescent growth occurs in the Formosan male is

$$x + 12 = -\frac{a}{b} + 12 = \frac{1.21071}{0.44726} + 12 = 14.707$$

$$= 14 \text{ years and } 8.5 \text{ months.}$$

Similarly, the age of maximum rate of adolescent growth for the Formosan female is

$$x + 12 = -\frac{a}{b} + 12 = \frac{1.06866}{0.59474} + 12 = 13.797$$

$$= 13 \text{ years and } 10 \text{ months.}$$

With a view to comparing the growth velocities at different ages, the curves of annual increments in the body weight of the Formosans are illustrated in figure 5.

After birth the velocity of growth begins to diminish at first rapidly and then gradually until between 4 and 5 years, both sexes always running roughly parallel with each other. It then rises by degrees, in such a fashion that the female exceeds the male all the time. At between 11 and 12 years in the female and between 12 and 13 years in the male, the velocity of growth rises abruptly and reaches a maximum at between 13 and 14 years in the female and between 14 and 15 years in the male, though the latter maximum is higher than the former. The point of maximum growth velocity corresponds to the point of inflection of the logistic cycle. It is conceivable that the starting point of this abrupt rise in growth velocity indicates the beginning of adolescence. The age of maximum rate of adolescent growth for each sex which has been theoretically calculated, can also be estimated graphically.

After this peak is reached, the velocity of growth diminishes at first slowly, then rapidly, and again slowly, till it practically reaches zero which indicates maturity or adulthood. After the age of maximum rate of adolescent growth is passed, the males always weigh more than the females. It is obvious from figure 5 that the age at which growth stops is 26 years for Formosan females and 31 years for Formosan males. Further gain in weight after these years may be considered as due solely to the deposition of fat, which does not involve increase in the number of tissue cells resulting from cell division. The curves in figure 5 make it clear that females mature earlier than males.

It is well known that the endocrine glands play a vital role in growth by a specific effect of their hormones on growing tissue and by their influence on the body's metabolism. The anterior pituitary secretes a specific growth hormone whose principal actions are accelera-

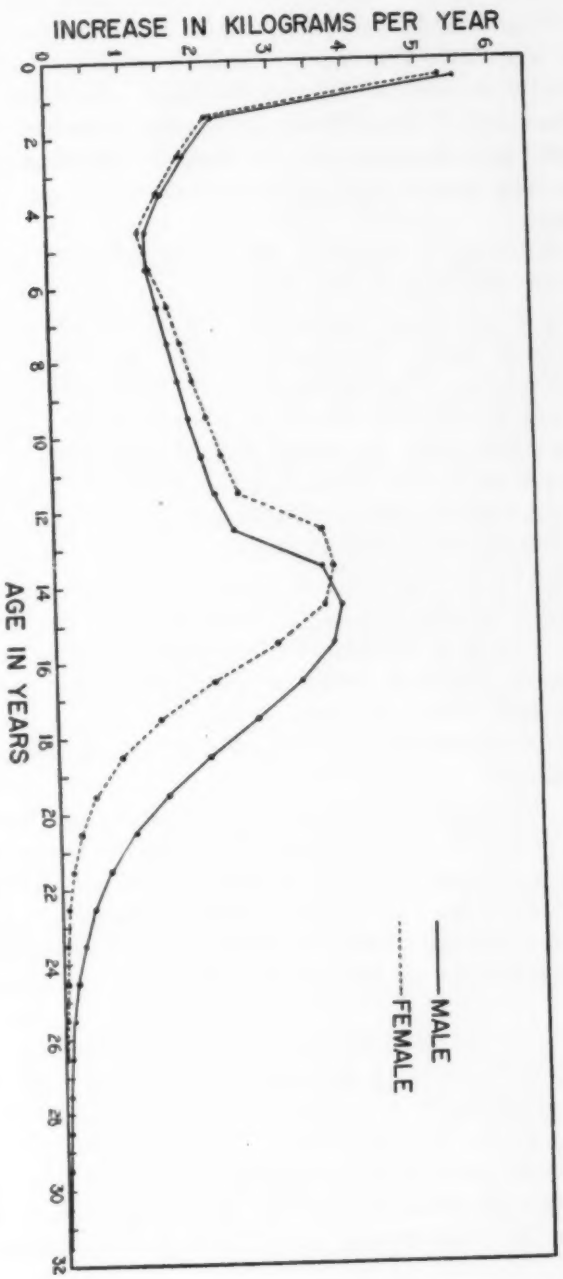

FIG. 5. ANNUAL INCREMENTS IN BODY WEIGHT OF FORMOSANS

tion of bone growth and tissue building. Less directly the gland influences growth by the action of its hormones on other glands of internal secretion. The thyrotropic hormone of the anterior pituitary regulates the secretion of thyroxine of the thyroid gland, which is probably second only to the pituitary in relative importance in its influence on growth and development. A normally functioning thyroid promotes skeletal growth, increases the metabolic rate and promotes sexual maturation.

The gonadotropic hormones secreted by the anterior pituitary cause the ovarian cycle and the secretion of ovarian hormones in the female, and bring about the spermatogenesis as well as the secretion of testis hormone in the male. The gonads are also necessary for proper development of the body. The importance of the parathyroid glands to normal growth and development can be appreciated from the fact that these glands are responsible for normal bone development.

It is well established (DeLee and Greenhill, '48) that the functions of the maternal anterior pituitary and thyroid glands are increased during pregnancy and gradually return to normal after childbirth. The fetus which has been growing at an accelerated rate under the influence of the various growth-inciting hormones from the mother's blood, slows down the velocity of its growth after birth (see figure 5), presumably for the reason that these hormones come to the infant only insufficiently from the milk. As time goes by, the child's own endocrine glands gradually increase their functions, so that the velocity of growth rises correspondingly.

When the function of the anterior pituitary and thyroid glands is increased so greatly as to stimulate the sex glands, the velocity of growth is sharply accelerated. This is the onset of adolescence which is to be followed before long by puberty or sexual maturation. As can be seen from figure 5, the age of onset of adolescence is between 11 and 12 years in the Formosan female and between 12 and 13 years in the Formosan male.

Puberty begins when the sex glands become mature as a result of continuous stimulation by the anterior pituitary and thyroid hormones. The first menstruation is generally recognized as an objective indicator of puberty in the female, while in the male there is no marked sign, except for the onset of nocturnal emissions which does not necessarily coincide with the onset of puberty. According to S. R. Ko ('33) and K. E. Ko ('33), the average age of the first menstruation in the For-

TABLE 4

Solution of the Problems Proposed

PROBLEM NO.	SOLUTION			
I	First Cycle: Catalytic Growth Period for Formosans; from birth to 9 months Second Cycle: Catalytic Growth Period for Formosans; from 9 months to 5 years Third Cycle: Compound Interest Growth Period for Formosans; from 5 years to 13 years Fourth Cycle: Logistic Growth Period for Formosans; from 13 years onwards			
II	Birth Weight:	Male Female	3.191 Kilograms 3.097 Kilograms	(see table 3)
III	see table 3			
IV				
V				
VI				
VII	Maximum Limit of Growth:	Male Female	53.5 Kilograms 47.5 Kilograms	
VIII	Age of Onset of Adolescence:	Male Female	between 12 and 13 years between 11 and 12 years	(see figure 5)
IX	Age of Maximum Rate of Adolescent Growth:	Male Female	14 years and 8.5 months 13 years and 10 months	(see figure 5)
X	Age at which Growth stops:	Male Female	31 years 26 years	(see figure 5)

mosan female is 14 years to 14 years and 8 months. This is nearly the age of maximum rate of adolescent growth in the Formosan female that has been mentioned previously. It would seem that at the onset of puberty the velocity of the adolescent growth is at its maximum. In other words, the advent of pubescence is preceded by an acceleration, and followed by a retardation of growth in weight in the two sexes.

The problems proposed in table 1 are already solved by the results and discussion in the present study; the solutions to these problems are summarized in table 4.

SUMMARY

In order to solve problems which are of practical importance in various branches of medical science, a mathematical analysis of the human growth in weight has been carried out with special reference to the growth of the Formosans. Data about 87,277 Formosan males and 83,376 Formosan females, collected from 1938 to 1950, have been used in the present investigation.

It has been found that the growth of man has 4 cycles from birth to maturity. Both the first and the second growth cycles obey the law of catalytic reaction, except for the difference in rate of growth between the two cycles. The third growth cycle is ruled by the law of compound interest in Nature, whilst the fourth growth cycle follows the logistic law that describes the growth of human populations. These 4 cycles pass from one to the other with gradual transition.

The mathematical procedure for the analysis of the human growth curve has been thoroughly described, and the periods and equations of the 4 cycles for the two sexes of the Formosans have been calculated with accuracy.

The body weights at different ages of the Formosan male and female computed from the equations obtained were found to yield excellent agreement with the observed data from birth to maturity.

The ages for the onset of adolescence and the maximum rate of adolescent growth among Formosans of both sexes, as well as for physical maturity, have been determined; and the maximum limits of growth that Formosan males and females may reach in their lifetime, have also been calculated.

The changes in the growth velocity throughout the whole period of body development have been discussed from the endocrinological point of view.

Appreciation is expressed to Professor William G. Cochran, School of Hygiene and Public Health, Johns Hopkins University, for his suggestions and criticisms in the preparation of this paper.

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